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ABSTRACT

An approach to the use of computer assisted instruction (CAI) for teaching psychopharmacology is presented. A project is described in which, using the TUTOR programing language on the PLATO IV computer system, several computer programs were developed to demonstrate the concepts of aminergic transmitters in the central nervous system. Response characteristics of a simulated patient treated with psychopharmacological drugs are discussed, together with some of the advantages and disadvantages of TUTOR for such teaching situations. A flow chart of a computer lesson in this field is also provided, and alternative methods of presenting a problem are considered. (DGC)

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COMPUTER-ASSISTED EDUCATION SYSTEM

FOR

PSYCHOPHARMACOLOGY

By

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ABSTRACT

This dissertation sets forth a combination of the specific logic of Computer Assisted Education with the science of Psychopharmacology. Several Computer Assisted Education (CAE) systems are cited as well as computer languages for application by these systems.

An inquiry teaching method is used to develop several computer programs demonstrating aminergic transmitters in the central nervous system and finally a simulated patient with varying responses to psycho-pharmacological drugs. The flexibility and effectiveness of this type of instructional device for training difficult technical skills is cited in various references. The need is shown for this particular application of CAE in other references.

The TUTOR language is discussed in regards to its several applications and advantages. This includes basic aspects as well as a flow chart of a computer lesson displaying "computer logic". This shows a method of presenting a problem, with its teaching strategy, the possibility of various branching conditions, and eventually, how these can be solved. The solutions may vary due to the individuality of students involved.

Finally, the newly surfacing problems in the evaluation of training of psychiatric residents, and medical students, indicates the need for more intensive teaching methods.

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BIOGRAPHIC SKETCH

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PROLOGUE

Although there are no short cuts to the process of learning, Computer-Assisted Instruction (CAI) or Computer-Assisted Education (CAE) provides a highly individualized form of instruction.

There are many computer-assisted instruction programs or systems being developed, researched and updated for general educational needs, and these few are cited as examples:

The Tic-cit system (time-shared interactive, computer controlled information television) being developed by Mitre Corporation, in collaboration with the University of Texas and Brigham Young University. The Tic-cit program, developed under the direction of Victor Bunderson, adopts a formalized method of developing CAI "courseware" through the collaborative efforts of teams of programmers, educational psychologists and specialists in the subject of the course and is designed around small computers with self-contained package hardware operating programs and such course materials as is necessary for each school involved in the program.

The Plato Program (programmed logic for automatic teaching operations) being developed by the University of Illinois at Urbana. The research, directed by Donald Bitzer, espouses an approach of letting teachers design their own program with the aim of improving the productivity of teachers and the effectiveness of the educational process. Chapter I expands further on this program.

The University of Illinois Medical Center in Chicago has another program termed Coursewriter III, designed by IBM. This has been physician oriented in basic subjects, and may prove valuable for author technic variation, since it is used in many fields. Author technic is the technic of lesson writing for various subjects and the originator is considered the "author."

Computer languages are as diverse as the many types of equipment being devised and the multitude of designs for similar applications.

This dissertation is an attempt to indicate the value of Computer-assisted Instruction as it applies to some aspects of Psychopharmacology. This education format for Psychopharmacology is further limited to basic concepts of neurosynaptic transmission, transmitter substances and how various drugs affect these transmitters. These concepts and substances are elaborated on in Chapters IV, V, and VI. The computer programs to introduce the student to basic neurosynaptic transmissions are demonstrated in Appendix B. The computer program for information in instruction regarding transmitter substances is contained in Appendix C. A simulated patient with responses to student treatment is contained in Appendix D.

CHAPTER I

INTRODUCTION

This author has participated in discussions about methodology and observed a need for changing the present method of teaching Pharmacology, and Psychiatry and the method of adequately presenting the present day available information. Drug use is a part of our cultural history, and the understanding of presently used drugs is necessary to evaluate the change now occuring (ref. 9, 38).

The purpose of this dissertation is to propose a combination of tutorial-inquiry teaching strategy to permit the student to gather data, perform simulated experiments, and then respond to questions.

The goals of this project are: 1) to write and adapt basic course material for use in a computer based teaching system; 2) to incorporate the inquiry teaching method (ref. 8) into the course prepared for use on the computer based teaching system; 3) to develop and program a generalized inquiry teaching logic for PLATO (fig. 7); 4) to illustrate how the basic course material can be taught effectively by a computer-based teaching system; 5) to determine if the course prepared for use on computer-based teaching system can be beneficial to the curriculum.

It is important to stress flexibility and a problem-solving approach to an educational series in order to satisfy the requirements of the several types of students who may require the use of the PLATO system. In preparing the course material, the logic necessarily must be flexible in order to present material in a variety of ways.

There are many advantages to the use of a computer assisted education system such as PLATO. The PLATO system has many features which make it an ideal instructional device for training in difficult technical skills. The rapid response and internal branching capabilities of the system provide each student with immediate attention and individualized instruction. Although servicing many students simultaneously, the response to request and feedback of results is so rapid that most students receive the impression that they have the computer's undivided attention. The use of computer internal branching allows the method of presentation or type of material to be altered on the basis of the last response and facilitates remedial instruction. In addition, the capability of simulating experiments which are otherwise time consuming, costly or dangerous is extremely valuable. For example, pharmacology students may experiment freely with simulated patients. Although some instructors find the idea of experimentation alarming, this concern is unfounded. Allowing a student to determine his own approach to a problem situation, to err and resolve problems in his own way is another method of teaching. It does not create a "devil-may-care" or other undesirable attitude in students which may affect the actual clinical situation. Rather, the student learns much by experimenting to find out "what happens if?", and in this manner finds the errors in his judgement or solutions to pharmacology problems prior to the real-life situations. If inadvertent, his mistakes in judgement usually make a lasting impression, but fortunately, since simulated pateints are easily revived, the mistake does not result in trauma, emotional or physical, to either student or patient. Evaluatuion, both of and by students, is essential to continued effective instruction.

This system provides complete record keeping capability and allows authors to obtain immediate information concerning student performance. Data on student response are invaluable for diagnosing and revising lesson material and for locating individual student difficulties. Lessons are quickly and easily revised or updated. An important advantage of Computer-Assisted Education (CAE) is that it makes an efficient use of both instructor and student's time. Students can learn at their own pace; those requiring less time to complete the material are free to do independent study and to devote more time to other courses, whereas those students who need it can have additional instructional time without feeling that they are slowing down the class. The instructor has more time to provide individual instruction, communicate with students, answer questions, conduct discussions, organize, guide, and manage educational experiences. We look upon computer-assisted education more to supplement rather than supplant the teacher. There are many instances where the computer can and should replace the instructor, releasing them for those aspects of teaching where the human instructor is more efficient and effective than the computer. A computer-assisted education system can dispense information effectively, and in microseconds (ref. 6). PLATO is an excellent device for providing drill and practice, and accomplishes tedious and time consuming tasks of testing and grading with ease and rapidity. Its use should not be limited to this however, because it can also be used effectively to teach concepts and problem solving. There are two other advantages of CAE which are of particular importance to education today. First, it lends stability to situations where there is a shortage or rapid

turnover of faculty, and secondly, it allows larger numbers of students to be taught effectively without a comparable increase in faculty (ref. 1). The computer furnishes the student with written or 35 mm slide information and processes the responses of the student, and tabulates results immediately for use later.

A description of Computer-Assisted Education System: PLATO IV

PLATO, the computer-based teaching system located at the University of Illinois' Computer-based Education Research Laboratory was utilized for this project, using terminals at the University of Illinois Medical Center and terminals at the University of Illinois Circle Campus.

In the pharmacology material, the computer presents the student with simulated patients, problem situations, and questions, and provides, via a graphic and pictorial display, the information necessary to solve the problems or answer the questions as indicated in Appendix B, C, & D. This information is prestored in and calculated by the computer and given back to the student in response to inquiries (fig. 6). The student, by means of the computer-connected terminal, simulates experiments, gathers data, and answers the questions.

The PLATO System

PLATO is a computer-based teaching system which utilizes a computer. The students are all members of an interactive team. The teacher designs the instructional material, and the computer presents this material to the students while monitoring and evaluating their performance. Each student can work at his own pace with access to

special information and help when problems arise. Student interaction with the computer provides information on lesson effectiveness. The lesson material can be easily revised by the teacher in order to modernize or improve instruction. PLATO frees the teacher for special work with students, an advantage which conventional does not usually include.

The most recent version of the PLATO teaching system is known as PLATO IV. The system employs terminal equipment (hardware) and computer programming (software). A recently (1975) increased storage capacity change has necessitated an interruption of partial service. The development and testing of the system have spanned thirteen years. PLATO IV terminals can be found not only in the University of Illinois campus at Urbana-Champaign, but in other nearby locations and at points as far away as the east and west coasts of the United States, and just recently some overseas terminals.

Features of PLATO

PLATO lessons are written to accommodate individual rates and styles of learning, as well as to provide a means for acceptance of student-constructed answers, immediate feed-back for student responses, and remedial or advanced instructional material.

Easy Production and Evaluation of Lesson Material

PLATO instructional material is written and edited on-line from any terminal while time-sharing the system with other authors and students. The author language is simple, though flexible and powerful. It includes a variety of graphic and computational capabilities, and

gives computer control of teaching style and strategy to the teacher. Production and revision of lessons are facilitated by a wide range of editing aids. Student performance may be automatically recorded and evaluated by the computer.

PLATO IV Equipment

A PLATO IV terminal consists of a keyset, which transmits the user's input (or request) to a central computer, and a display which can show simultaneously computer-generated written information and color slide to the user.

The PLATO IV terminals are controlled by a Control Data Corporation 6000 series computer system. Terminals are connected in groups of thirty-two to the computer over a single IV channel with a maximum capacity of one thousand terminals per channel. Extended computer core storage allows rapid access to large amounts of material for use by either students or authors. Magnetic disks contain a library of thousands of lessons. Auxiliary equipment, controllable by the computer, can be added to the PLATO IV terminal such as audio systems, touch panels, film projectors, tape recorders, electronic equipment for research, and laboratory experiments may be used.

Some Details of the PLATO IV Terminal

There is a visual display which is $8\frac{1}{2}$" square, transparent, flat glass plasma panel. The panel has 262,144 (512 x 512) individual digitally addressable points under computer control. It has a writing speed of 180 characters per second and 60 lines per second. With the capability of displaying up to 2,048 characters on the screen 256

immediately available characters (128 standard, 128 alterable) many unusual and interesting problems can be prepared. It also has inherent memory in the display panel. The response time 0.2 second to student input allows a rapid correction at any time. The slide selector has a back projector through plasma panel allowing superimposed slide image and display graphics. It has a capacity of 256 colored slides in microfiche format, randomly addressable by the computer.

Keyset

The keyboard module has standard typewriter characters plus special function keys.

Touch Panel (optional)

The touch panel has 256 positions (16 x 16) individual addressable positions by touch--under computer control.

Audio Equipment (optional)

The audio equipment has more than 4,000 random access messages totalling up to 21 minutes in length--under computer control, with an average access time of .5 second.

CHAPTER II

THE COMPUTER LANGUAGE TUTOR

TUTOR is a computer language that has been especially developed for instructional purposes. It compares to CAI language SILT (ref. 45) and the many others as suggested in the prologue.

TUTOR'S many functions is to assist the teacher in the instruction of students. TUTOR is based on a format similar to a way people might normally communicate and is thus, easily mastered. Using TUTOR, the instructor can program a computer to carry on a dialog with a student in such a way that the student is led, through his own reasoning, to correct answers or solutions to questions asked by the computer (programmed in), (see fig. 7) which is a diagram of Teaching Logic. If the student appears unable to reach the proper solution after several attempts, then the computer automatically displays the answer and if necessary explains the reasoning required to reach that solution. This type of dialog, through reliance on the student's own reasoning, can be an effective learning experience.

TUTOR has many features that are helpful to both the teacher and to the student. One feature of TUTOR is that it permanently records the student's name, the name of the lesson taken or being used, and the date the student takes each lesson or review. TUTOR is also capable of recording how well each student is progressing. It also records, as the student's option, comments during each lesson. These comments may form the basis of useful student feedback.

Branching is a feature that allows for different student abilities.

This feature allows the instructor to send the student to different material within the same lesson according to how well the student demonstrates understanding through responses to key questions; thus one student may be allowed to skip certain material if he demonstrates adequate understanding.

Basic Aspects of TUTOR

In their simplest form, lessons administered by the PLATO interactive educational system consist of a repeating sequences: a display on the student's screen followed by the student's response to this display. The display information may consist of sentences, line drawings, graphs, animations (moving displays) - nearly anything of a pictorial nature - and in any combination. The student responds to this display by pressing a single key (e.g., the HELP or NEXT key) or by typing a word, sentence, or mathematical expression, or even by making a geometrical construction. Lesson authors provide enough details about the possible student responses so the PLATO can maintain a dialog with student. The sequence of a display followed by a response is the basic building block of a lesson and is called a "unit" in the TUTOR language. This "display-response" terminology is convenient but is not intended to imply that the student is in a subservient position. Often, what we will conventionally call the student "response" is a question or a command to PLATO to respond with a display of some kind.

An author constructs a lesson by writing one "unit" at a time. For each unit, the author uses the TUTOR language to specify (1) the display that will appear on the student's screen, (2) how PLATO is to

handle student responses to this display, and (3) how the current unit connects to other units.

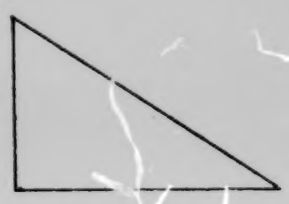
A statement written in the TUTOR language appears as follows:

```
write      How are you today?
```

command tag

The first part of the statement (-write-) is called the command, while the remainder (How are you today?) is called the tag. Command names mnemonically represent PLATO functions. Following is an entire unit written in TUTOR. The figure shows what a student would see on his screen while working on the unit.

```
unit     geometry
at       1812
write    What is this figure?
draw     51Ø;151Ø;154Ø;51Ø
arrow    2Ø15
answer   it,is,a  (right,rt) triangle
write    Exactly right!
wrong    it,is,a  square
write    Count the sides!
```



As one can infer, tags individualize commands for the particular function desired. We will discuss each statement of this unit in detail.

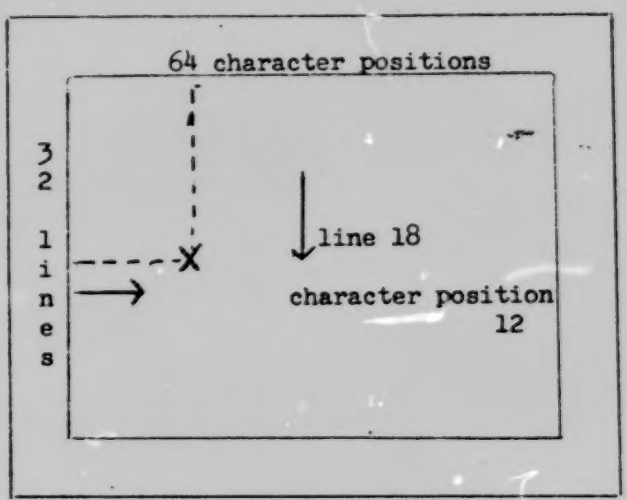
```
unit     geometry
```

The -unit- statement initiates each unit. The tag (geometry) will become useful later when units are connected together to form a lesson. Each unit must have a name. No two units in a lesson may have the same name.

```
at       1812
```

The -at- statement specifies at what position on the screen a display will occur. The tag "1812" means that we will display some-

thing on the 18th line in the 12th character position. The top line of the screen is line 1 and the bottom line is line 32. There are 64 character positions going from Ø1 at the left edge of the screen to 64 at the right. Thus, 1Ø1 refers to line 1, character position Ø1 (the upper left corner of the screen), while 3264 refers to line 32, character position 64 (the lower right corner of the screen). Note that "Ø" means the number zero, as distinct from the letter "O".



write What is this figure?

The -write- statement causes the text contained in the tag to be displayed on the student's screen. The writing starts at line 18, character position 12, as specified by the preceding -at- statement.

draw 51Ø;151Ø;154Ø;51Ø

The -draw- statement specifies a straight-line figure to be displayed on the screen. In this particular case a series of straight lines will be drawn starting at location 51Ø (line 5, character position

1Ø), going vertically downward to location 151Ø; then to the right to location 154Ø, and finally back to the starting point, 51Ø. This produces a right triangle on the student's screen.

```
arrow     2Ø15
```

The -arrow- statement acts as a boundary-line that separates proceding display statements from following response-handling statements. Thus, what precedes the -arrow- command produces the screen display which remains visible, while the student works on the question. Statements after the -arrow- command are used in handling student responses to the display. In addition, the -arrow- statement notifies TUTOR that a student response is required at this point in the lesson. The tag of the -arrow- statement locates the student response on the screen. An arrowhead is shown on the screen at this place to indicate to the student that a response is desired and to tell him where the response will appear. In this case, the arrowhead will appear on line 2Ø, character position 15. The student's typing will start at 2Ø17, leaving space between the arrowhead and his first letter.

```
answer  <it,is,a> (right,rt) triangle
.
.
.
.
wrong   <it,is,a> square
```

The -answer- and -wrong- statements are used to evaluate the student's response. The special brackets < and > enclose optional words, while the parentheses enclose important words which are to be considered synonums. Thus, any of the following student responses would match the -answer- statements: "a right triangle", "it is a rt triangle", "rt triangle", etc.

If the response matches the tag of the -answer- statemtn, TUTOR writes "ok" after the student's response. For a match to a -wrong- statement, "no" is written. An "ok" judgement allows the student to proceed to the next unit, whereas a "no" judgement requires the student to erase and try again. Any response not foreseen by -answer- or -wrong- statements is judged "no".

Having matched the student's response, TUTOR proceeds to execute any display statements following the matches -answer- or -wrong- statement. Thus, student responses of "a right triangle" and "square" will trigger appropriate replies. In the absence of specific -at- statements, TUTOR will display these replies three lines below the student's response on the screen. Here is what happens if the student responds with "a lovely triangle, right?":

```
> a lovely  tringle, right?
  XXXXXX  ======= <
```

TUTOR automatically marks up the student's response to give detailed information on what is wrong with the response. The word "lovely" does not belong here and is marked with XXXXXX, the word "tringle" is misspelled and is underlined, and the word "right" is out of order, as is indicated by the small arrow.

CHAPTER III

COMPUTER LESSON CHARACTERISTICS AND EVALUATION

Computer Interaction

Each problem is initiated by a brief presentation revealing only those aspects of the situation which the participant would have immediately available. The examinee must then decide how he will approach this problem. He is therfore offered a choice among several general type of inquiry and/or actions that might plausibly be pursued at that point in the problem. He decides which type of inquiry or action to pursue first and records his decision by typing his answer at the arrow (see fig. 6).

Each problem contains many sections, each section devoted to a general type of inquiry or action that might be appropriate at some stage in the solution of the problem. The sections are usually arranged in scrambled order to avoid suggesting any preferred sequence of actions to the examinee. In fact, some sections are not necessarily relevant to the optional resolution of the problem but are included to provide examinees with a range of possible activities.

Within each section the examinee is confronted with a list of specific inquiries or actions of the general type he is seeking. Again he records each decision or action he selects. On the basis of these new data he must decide upon the next step he wishes to take and again records that decision to obtain instructions directing him to the next appropriate section of the problem. In other words, in each general section the examinee must indicate his decisions about a series of specific requests or actions. At the end of each

section he must then make a strategic decision about his subsequent approach; this decision determines the section of which he is next directed. In this fashion a problem may be carried through many stages, at each of which the examinee must make further decisions based on the specific responses evoked by his own earlier decisions.

The stages in the problem and the responses to the specific procedures the examinee may elect are meticulously designed to simulate an actual situation, examples in Appendix D. In so far as possible, results of specific inquiries and actions are presented in the form in which they occur in real life; thus, tabular, graphic, diagrammatic, pictorial and other methods of reporting are used to supplement verbal presentation of results. No interpretation of these data should be offered and none is explicitly demanded of the examinee, he is merely given the data he requests and is required to act on them as he would in the real setting.

The complications which must be managed may differ from examinee to examinee depending (as they do in life) on the unique combination of specific procedures each has elected at earlier stages. For some, the responses will reveal an instruction to skip entirely one or more sections of a problem because the approach they have chosen is effective in avoiding potential complications with which others must cope. If, however, at any stage the examinee elects procedures that are detrimental, or fails to take measures indispensable to a satisfactory resolution of the problem, he may be directed to a special section of the problem where he has the opportunity to take steps to rectify his previous errors; if these remedial measures are inadequate, he may at

that point be told that the problem is terminated because of insoluble complications (he ran out of time, the patient died, or whatever the author of the program desires to use).

Description of Problem for Presentation to Student

A written problem is introduced by a statement followed by stages in the evolution and resolution of the problem. The opening serves to define the initial situation, identify the examinee's role, specify his task and indicate the resources he can call on and the constraints under which he will be working.

Following the opening statement, the examinee is directed to the initial section of the problem where he finds a list of alternatives from which he must choose his first approach. His choice produces a response that yields feedback on the consequences of his inquiry or action (Fig. 7). Though the basic organizing principle may differ from problem to problem, the use of a single concept for organizing each of the sections of a problem is an important characteristic of a written problem (questions during a selected interview should be kept together in a section, questions directed to a student in another section, etc.).

Each section of a written problem contains two distinct parts: 1) a list of specific inquiries or actions (the options) and 2) a list of broad strategic alternatives that constitute a bridge to the next sections. These two constituents--an option segment and a bridge segment are essential elements in every section of every written problem.

In each section, each segment is preceded by an instruction which informs the examinee what he is to do in that segment; to choose among a series of specific actions or inquiries (option segment) or to make a broad decision which determines the next section to which he is directed (bridge segment). The option segment consists of possible inquiries or management decisions the examinee may wish to make. The bridge segment will take one of two forms; it may consist only of a single statement directing the examinee to the next section, or it may consist of a list of broad strategic alternatives from which the examinee is directed to select his next step. Such alternatives in a bridge segment are called branches. When the examinee makes his choice from among the branches, the appropriate response will give him an instruction directing him to the next section.

Taken together, the options and branches constitute the items in a written problem; all of the information and instructions provided as feedback to these items are called responses, whether they are in the form of data or directives and irrespective of where they are placed.

Responses by the computer on the visual panel serve two purposes. Their immediate function is to provide feedback to the examinee either in the form of information about the results of the inquiries and actions he has chosen or in the form of directions for proceeding through the problem. Subsequently, the responses provide the test scorer with a PLATO record of the decisions the examinee has made--a record in a form which makes it impossible for the examinee to retract a

decision that he finds to have been ill-advised.

Preparing Written Problems for use on a PLATO Terminal

Selecting the Problem. The two reasons for assessing problem-solving skills, are: 1) Information and consequence of actions evoked by the examinee's choices are immediately available to him to assist him in making subsequent decisions, and 2) He has considerable freedom to chart his own course in resolving the problem. The type of situation that is best adapted to this technique is one in which effective decision-making depends on the ability to gather and interpret data and to discriminate between appropriate and inappropriate actions, and in which ample opportunity is provided for the examinee to make decisions and re-evaluate the situation at several stages in attempting to resolve the problem. In general, the problems most amendable to this technique are those in which there are several phases of data collection, each necessarily followed by some action, the property of which depends on data obtained earlier.

Among the many problems that meet these criteria, the only ones suitable for development as problems for a visual display panel are those related to the specific subject and skills which are intended to be assessed. Thus, it is necessary first to define what to assess and then select a problem that addresses itself directly to that assessment. Selection of a problem often involves a process of comparing the outline of the proposed problem against your objectives until the two are congruent.

Blocking out the Problem. Once the problem has been selected for development, it is necessary to outline or "block out" the sequence

of events that will occur in the course of the evolution of the problem from the first stages of data collection to the final resolution of the problem. At this stage in the construction of the written simulation, it is also necessary to consider the kinds of errors that examinees may make in attacking and resolving the problem and to determine the consequences that will ensue from each of these errors. Thus, in blocking out the problem the author will develop a scenario much like that which a novelist or a playwright develops. However, in addition to the main "story line" he will need to outline alternate sequences of events that will occur should the problem-solver take the wrong turn at any point. Finally, he will have to determine how the problem is to be terminated for all variation of the "story".

Developing an Opening Scene. Once the main component parts of the problem have been blocked out and the sequence of events determined, it is necessary to consider exactly how the problem is to be introduced to the examinee. What is the setting of the problem? What information is immediately available? What role is the examinee to assume, and what is his specific taks in the situation? In short, how is the problem to be presented so that the examinee is in an appropriate position to make his first set of decisions?

Organizing the Data Required in the Problem. If the problem is to assess data gathering skills as well as decision-making skills, it will be necessary to give the examinee opportunity to obtain data from a wide variety of sources. Once the author has determined the specific content of the problem, has blocked out the sequence of events, and has

identified the data to be incorporated in the opening scene, it is necessary for him to determine what general types of data sources should be available to the examinee at various points in the problem and the types of information that these data sources would be likely to supply. This determination must address itself not only to the data required for the examinee to clarify and solve the problem; it must also provide appropriate sources of corrective feedback on the consequences of inappropriate or even destructive inquiries and actions that an erring examinee might select.

Developing Sections. Once the data sources and the types of information to be obtained from each have been determined, the problem author is ready to develop the several sections that will compose the problem. Each of these will contain many items that give the examinee an opportunity to make numerous inquiries and to take any number of specific actions. These specific inquiries and actions constitute the option segment of a section.

Bridging Between Sections. Once an examinee has made all the inquiries and taken all the actions which he wishes to select from a given section, he must be directed to the next appropriate section of the problem. Problems which require all examinees to progress from one section to another in exactly the same sequences are called linear. Problems in which examinees are allowed to follow differing sequences are called branched problems. Variations in the sequences which examinees follow may be occasioned either because the unique configurations of decisions they make have different consequences (forced branching) or because the examinee themselves select different attack strategies (free branching).

Refining the Problem. Once a problem has been developed, review, editing and polishing should be undertaken by the problem author, by other specialists in the problem's content, by a measurement specialist, and by a proofreader. Whenever possible, the problem should be pretested in pilot form and the reactions of examinees should be sought, especially regarding the problem's realism. Having obtained evaluations of the original problem, the author should make evaluations of the original problem and make whatever refinements would improve the problem, repeating the review and refinement until he is confident that the problem achieves the purpose for which it was developed.

If a problem is to be used in assessing the student's performance, it might also be desirable to devise a scoring system capable of describing levels of performance in numeric form. A scoring system should be subjected to the same rigorous review and revision process applied to the problem itself to insure the appropriateness of the measurements it yields. See Figures 3 through 7.

The following three chapters will be basic information which is to be utilized by students to be better prepared in an introductory study of Psychopharmacology. This information is then used and programmed into a PLATO IV computer using TUTOR language, see examples in Appendix B, C, & D.

CHAPTER IV

CONCEPT OF AMINERGIC NEUROTRANSMITTERS

Elliott first enunciated the concept of neural communication by means of chemical transmitters (ref. 17). Elliott's concept of chemical neurotransmission was accepted slowly. A neurotransmitter is a chemical that is discharged from a nerve-fiber ending. It reaches and is recognized by a receptor on the surface of a postsynaptic nerve cell of other excitable post junctional cell and either stimulates or inhibits the second cell (Fig. 8).

A variety of transmitters occur in neural tissue. For example, acetlycholine and norepinephrine function in the peripheral portions of the autonomic systems and it is assumed that these and other compounds are important as chemical mediators or modulators in the central nervous system (CNS).

The evidence for the transmitter role of a substance in the CNS has been indirect since most central synapses are inaccessible to direct study.

Today it is clear that many different neurotransmitters, hormones and neurohormones influence a variety of tissues and physiological processes. They are the agents through which the brain regulates movement and changes mood and behavior (ref. 12).

To be classed as a neurotransmitter, a chemical should fulfill a certain set of criteria. Nerves should have the enzymes required to produce the chemical; when nerves are stimulated, they should liberate the chemical, which should then react with a specific receptor on the post junctional cell and produce suitable biological responses; mechanisms should be available to terminate the actions of the

chemical study. On the basis of these criteria, two compounds are now established as neurotransmitters: acetycholine and noradrenaline. Nerves that contain them are respectively called cholinergic and noradrenergic nerves. There are a number of other nerve chemicals that meet many of the listed criteria but have not been shown to meet them all. These "putative" transmitters are dopamine, adrenaline, serotonin, octopamine, histamine, gamma aminobutryic acid, glutamic acid, aspartic acid and glycine. A popular theory is that these various transmitter substances are made in the neural structure from precursor amino acids.

The catecholamines include noradrenaline (norepinepherine), dopamine and adrenaline (epinephrine). They have in common a chemical structure that consists of a benzine ring on which there are two adjacent hydroxyl groups and an ethylamine side chain (Fig. 13a). In the brain, noradrenaline is present in amounts as listed (Table 3). In the brain noradrenaline acts as a neurotransmitter, that is, it exerts most of its effect locally on post junctional cells. In the adrenal medulla it functions as a hormone, that is, it is released into the bloodstream and acts on distant target organs. Dopamine, once thought to be an intermediate in the synthesis of noradrenaline and adrenaline may also be a neurotransmitter in its own right in the brain, where it function to modulate mood and behavior. The third catecholamine, adrenaline, may not be a transmitter and is concentrated in the adrenal medulla and is discharged into the bloodstream during states of fear, anger or other stress and affects the heart, the liver and other organs. Just in the past year it has developed that adrenaline is probably also a neuro-transmitter, since it is

found in nerves in the brain (ref. 4).

Techniques developed a decade ago in Sweden made it possible to visualize catecholamines in neurons directly, by the fluorescent glow they emit after treatment with formaldehyde vapor. Fluorescent photomicrography, electron microscopy and radioautography have revealed the structure and functioning of the symphathetic nerve cell in great detail. (See Fig. 9). The neuron has a cell body and a long axon, or main fiber, that branches into a large number of terminals. Each nerve ending is studded with varicosities, or swellings, that look like beads on a string, so that a single sympathetic neuron can innervate thousands of other "effector" cells. (ref. 12).

Synthesis and Release

The process leading to the synethesis of catecholamine transmitters begins in the cell body, which has the machinery for making the four enzymes needed for their formation: tyrosine hydroxylase, dopa decarboxylase, dopamine beta-hydroxlase (DBH) and phenylethanolamine N-methyltransferase (PNMT). (Fig. 13). The enzymes synthesized in the cell body are carried down the axon by a natural flowing process to the nerve endings, where the synthesis of the catecholamines is achieved.

The discharge of neurotransmitter from the nerve endings caps a complex series of events. When a nerve is stimulated, its membrane is depolarized, with sodium moving into the nerve as potassium comes out; the nerve signal propagates as a wave of depolarization that moves along the nerve axon to the endings. As Bernard Katz of University College of London first showed for acetylcholine, the depolarization causes a quantum-- a packet or spurt, as it were-- of the transmitter to be discharged from the nerve ending into the synaptic cleft.

Biochemical evidence recently obtained by Axelrod and others (ref. 4, 12) shows that noradrenaline is released from nerves in much the same way. The vesicles in the endings contain not only noradrenaline but also the enzyme, DBH, that converts dopamine into noradrenaline. When the sympathetic nerve is stimulated electrically, noradrenaline and the enzyme are released in about the same proportions in which they are present in the vesicles. The only way that could happen would be through the fusion of the vesicle with the outer membrane of the nerve, followed by the formation of an opening large enough to allow molecules of noradrenaline to be extruded along with the much larger molecules of the enzyme. Such a release mechanism is called exocytosis. The detailed events whereby the vesicle fuses with the neural membrane and makes an opening to discharge its soluble contents are uncertain, as is the subsequent fate of the vesicle. We do know that certain conditions prevent the release of noradrenaline and DBH. One is the presence of vinblastin, a compound that breaks down the protein structures in nerve cells called neurotubules. Another is the presence of cytocholasin-beta, a substance that disrupts the function of the contractile filament system in cells. A third is the absence of calcium. These findings suggest that the long tubelike protein structures may orient the vesicles to a site on the neuronal membrane from which the release occurs. It is well known that microfilaments in cells can be activated by calcium so that they contract. It is therefore possible that depolarization causes calcium to activate a contractile filament on the neural membrane, which thereupon contracts to make an opening large enough so that the soluble contents of the vesicle can be discharged.

The observation that DBH is released from nerves suggested to

Richard Weinshilboum that the enzyme might find it way into the bloodstream. He devised a sensitive assay for the enzyme and found it is indeed present in the blood, and went on the measure the amount of the enzyme (which is found specifically in sympathetic nerves) in a variety of disease states. It is low in the hereditary disorder of the autonomic system called familial dysautonomia and in Down's syndrome (mongolism), and it is high in torsion dystonia (a neurological disease involving muscle spasticity), in neuroblastoma (a cancer of nervous tieeus) and in certain forms of hypertension. The findings suggest that in each of these diseases there are abnormalities in the functioning of the sympathetic nervous system.

Action and Inactivation

Once the neurotransmitter is liberated it diffuses across the cleft between the nerve terminal and adjacent cells. The capacity of a neighboring effector cell to respond to the transmitter then depends on the ability of a receptor on the post-junctional cell's surface to selectively recognize and combine with the neurotransmitter. When the receptor and transmitter interact, a series of events is triggered that causes the effector cell to carry out its special function. Some of these responses occur rapidly (in a fraction of a second), as in the propagation of nerve transmission across a synapse; others of intracellular enzymes. There are two receptors that recognize noradrenaline, alpha and beta adrenergic receptors and there is one for dopamine. These receptors can be distinguished from one another by the specific response each elicits and by the ability of specific drugs to block those responses.

The beta adrenergic receptors turn on an effector cell, and they do so by presence of adenosine 3'5" monophosphate, or cyclic AMP, the universal "second messenger" that mediates between hormones and many cellular activities elicited by those hormones. Investigators have traced several of the steps in the activation of the receptor by noradrenaline by studying the interaction of noradrenaline and fat cells or cells of the liver or of the pineal gland. The pineal, which makes a hormone called melatonin that inhibits the activity of sex glands, particularly suitable because it is heavily supplied with nerves containing noradrenaline (see reference 44). Melatonin is synthesized in a number of steps, one of which, the conversion of serotonin-N acetyltransferase. It is that enzyme's synthesis that is controlled by the beta adrenergic receptor. When noradrenaline is released from a nerve innervating the pineal, it interacts with beta adrenergic receptors on the outside of the membrane of the pineal cell. Once a receptor is occupied by noradrenaline, the enzyme adenylate cyclase, on the inner surface of the cell membrane, is activated. The adenylate cyclase then converts the cellular energy carrier ATP to cyclic AMP, which in turn stimulates the synthesis of serotonin N-acetyltransferase. This complex series of events can be turned off by propranolol, a drug that prevents the noradrenaline from combining with the beta adrenergic receptor.

Once the neurotransmitter has interacted with the post junctional cell, its actions must be rapidly terminated; otherwise it would exert its effects for too long and precise control would be lost. In the cholinergic nervous system the acetylcholine is rapidly inactivated by

the enzyme acetylcholinesterase, which metabolizes the transmitter. In the past 10 years, it has become clear that the inactivation of neurotransmitters through enzymatic transformation is the exception rather than the rule. Catecholamine neurotransmitters are metabolized by two enzymes, catecho-O-methyltransferase (COMT) and monoamine oxidase (MAO) (Fig. 16): the latter is a particularly important enzyme that removes the amino (NH_2) group of a wide variety of compounds, including serotonin, noradrenaline, dopamine and adrenaline. There are enzyme-inhibiting chemicals that can prevent COMT and MAO from carrying out their biochemical transformations; when such inhibitors were administered to animals the action of noradrenaline was found still to be rapidly terminated. It is postulated that noradrenaline is rapidly inactivated through its recapture by the sympathetic nerves; once it is back in the nerves, of course, the neurotransmitter cannot exert its effect on post junctional cells. Leslie L. Iverson of the University of Cambridge has since shown that this neuronal recapture by sympathetic nerves is highly selective for noradrenaline or compunds resembling it in chemical structure (ref. 46). Recent work indicates that uptake by nerves may be the most general mechanism for the inactivation of neurotransmitters. (Fig. 18).

Regulation

Chemical transmitters in sympathetic nerves (and presumably in other nerves) are in a state of flux, continually being synthesized, released, metabolized and recaptured. The activity of nerves can also undergo marked fluctuation during periods of stress. In spite of all these dynamic changes, the amount of catecholamines in tissues remains constant. A variety of adaptive feedback mechanism alter the forma-

tion, release and response of catecholamines. There are fast regulatory changes that require only fractions of a second and slower changes that take place after minutes or even hours.

When sympathetic nerves are stimulated, the conversion of tyrosine to noradrenaline in them is rapidly increased (fig. 12). The increased nervous activity specifically affects tyrosine hydroxlase, the enzyme that converts tyrosine to dopa, because the enzyme's activity is inhibited by noradrenaline and dopamine. Any increase in nerve-firing brought on by stress, could and certain drugs lowers the level of catecholamines in the nerve terminals. This reduces the negative-feedback effect of noradrenaline and dopamine on tyrosine hydroxlase, so that more tyrosine is converted to dopa, which in turn is converted to make more catecholamines. Conversely, when nerve activity is decreased, the catecholamine level rises, slowing down the conversion of tyrosine to dopa by once again inhibiting the tyrosine hydroxylase (fig. 13, 13a).

Another rapid regulation is accomplished at the nerve terminal itself, where the alpha adrenergic receptors are situated. When the alpha receptors are activated, they diminish the release of noradrenaline from presynaptic nerve terminals into the synaptic cleft. When too much noradrenaline is released, it accumulates in the synaptic cleft; when the catecholamine level is high enough, it activates the alpha receptors on the presynaptic nerve terminals and shuts off further release of the neurotransmitter. (Fig. 25a).

A slower regulatory process is brought on by prolonged firing of sympathetic nerves, which can step up the manufacture of the catecholamine-synthesizing enzymes tyrosine hydroxylase, dopamine beta-hydroxylase (to a lesser extent) phenylethanol-amine N-methyltransferase (PNMT): the rise in the enzyme level enables the nerves to

make more neurotransmitter. This phenomenon of increased enzyme synthesis when animals are given reserpine, indicates a drug that lowers the blood pressure and incidentally increases sympathetic-nerve firing (which tends to raise the pressure). The reserpine brought about a gradual increase in tyrosine hydroxylase and DBH in sympathetic nerves and the adrenal gland and of PNMT in the adrenal gland. Increase in these enzyme were also found in animals exposed to stress, cold, physical restraint, psychosocial stimulation or insulin injection. When the synthesis of proteins was prevented by drugs, on the other hand, there was no elevation in enzyme activity after reserpine was given. This indicated that increased nerve activity stimulates the synthesis of new molecules of tyrosine hydroxylase, DBH and PNMT; with a greater need for neurotransmitters there is a compensatory increase in the synthetic enzymes that catalyse the making of these transmitters.

Sensitivity

In 1885 the German physiologist J. L. Budge observed that when the nerves leading to a rabbit's right eye were destroyed, the pupil of that eye became more dilated than the left pupil. The phenomenon was later explained by the American physiologist Walter B. Cannon, who postulated that as a result of denervation the effector cells somehow become more responsive. He called this effect the "law of denervation supersensitivity." Subsequent work showed that denervation supersensivitity is caused by two separate mechanisms, one presynaptic and the other postsynaptic. When nerves are destroyed, presynaptic inactivation by recapture is abolished, thereby leaving existing neurotransmitters to react with the postsynaptic site longer.

Denervation also causes a profound change in the degree of activity

of the postjunctional cell. Recent work with the pineal gland has suggested a hypothesis for supersensitivity, and also for subsensitivity, in postjunctional cells (reference 44). Noradrenaline stimulates the synthesis of the enzyme serotonin N-acetyltransferase through a beta adrenergic receptor in the postjunctional pineal cell. When the nerves to pineal cells are destroyed (or depleted of noradrenaline by the administration of reserpine), the pineal cells becomes 10 times as responsive to noradrenaline; that is, when the postjunctional cell is deprived of its neurotransmitter for a period of time, it takes just the same increase of N-acetyltransferase in the cell as 10 packets of transmitters would cause in a normally innervated cell. If, on the other hand, the pineal cell is exposed to an excessive amount of catecholamines for a period of time, it becomes less responsive; a larger amount of the transmitter is required to produce the same increase in N-acetytransferase.

These experiments suggest that changes in the responsiveness of excitable cells are the result of an alteration in the "avidity" with which the receptor binds the neurotransmitters. If the receptor is exposed to small amounts of catecholamine for some time, it reacts with the neurotransmitter easily; if too many neurotransmitter molecules bombard the receptor, it becomes less responsive. Depending on the tissue, this change in sensitivity can come within hours or days, so that it is an effective adaptive mechanism for excitable cells. It is possible that the tolerance that is often developed to a drug taken in excess may reflect subsensitivity on the part of cells that respond to the drug.

Role in the Brain

The brain has billion (10^{10}) of nerves that talk to one another by means of neurotransmitters. Neurobiologists are just beginning to unravel the complex biochemistry and physiology of chemical transmission in the brain. Many different neurotransmitters function in brain neurons, but because there are more precise methods of measuring catecholamines and drugs are available that perturb their formation, storage, release and metabolism, we know more about brain catecholamine than about the other neurotransmitters. Fluorescence photomicrography and drugs that selectively destroy catecholamine-containing nerves have made it possible to locate the noradrenaline, dopamine and serotonin cell bodies and trace the pathways of their axons and nerve endings. The cell bodies of the dopamine-containing nerves are in the area of the brain stem called the substantia migra, whence the dopaminergic axons course through the brain stem, many of them terminating in the caudate nucleus. The dopamine-containing tracts in the caudate nucleus play an important role in the integration of movements. (Fig. 24).

The elucidation of the biochemistry and pharmacology of dopamine in the brain has led to the development of a powerful treatment of a crippling disease. Parkinsonism. The Swedish pharmacologist, Arvid Carlsson, noted in 1959 that when reserpine was given to rats, it sharply reduced the dopamine content of the caudate nucleus in the brain and also caused a Parkinson-like tremor (ref. 11). The administration of dopa, a dopamine precursor that can get from the blood into the brain more easily than dopamine, abolished the tremors. These findings prompted Oleg Hornykiewicz, who was then working at the University of Vienna, to measure the content of dopamine in the brain of patients who had died of

Parkinson's disease. He found that there was virtually no dopamine in the caudate nucleus. The finding led directly to a major therapeutic advance by George C. Cotzias of the Brookhaven National Laboratory; when dopa, the dopamine precursor that can cross the blood-brain barrier, is administered, it makes up the dopamine deficiency and effectively relieves the symptoms of Parkinson's diesease. This is a good example of how basic research can sometimes lead rapidly to a new treatment for a disease.

There are two main tracts containing noradrenaline in the brain, the dorsal and ventral pathways. (Fig. 24a). The cell bodies of the noradrenaline-containing tracts are found in the lower part of the brain in the area called the locus ceruleus (ref. 4). Noradrenaline-containing nerve tracts are highly branched and reach many parts of the brain. Among the areas they innervate are the cerebellum and the cerebral cortex, structures concerned with the fine coordination of movement and alertness. Another part of the brain innervated by noradrenaline-containing neurons is the hypothalamus, which controls many visceral functions of the body such as hunger, thirst, temperature regulations, blood pressure, reproduction and emotional behavior. Manipulation of the noradrenaline levels in the brain can change many of the functions of the hypothalamus, particularly the "pleasure" centers. Noradrenaline tracts also appear to be involved in the mood elevation and depression. Recently nerves containing adrenaline have also been observed in the brain stem. The next few years should show whether these adrenaline-containing tracts also control emotion, mood and behavior.

Drugs have been powerful tools for probing the action of neurotransmitters. As our knowledge concerning neurotransmitters has

broadened, so has our understanding of the action of drugs on behavior and on the cardiovascular and motor systems; the two trends have interacted nicely. In the early 1950's, pharmacologists recognized that the hallucinogenic agent lysergic acid diethylamine (LSD) not only resembles serotonin in chemical structure but also counteracts some of its pharmacologic actions (by occupying sites intended for serotonin). Several workers therefore, proposed that serotonin must have something to do with insanity. Other hallucinogenic agents such a mescaline and amphetamine, on the other hand, are related in structure to noradrenaline. In the mid 1950's clinical investigators were learning that chemicals such as chloropromazine could mitigate psychotic behavior, and that monoamine oxidase inhibitors and imipramine and related drugs could relieve depression. At about the same time, it was observed that reserpine, which was proving valuable not only in the therapy of hyptertension but also schizophrenia, markedly reduced the levels of noradrenaline and serotonin in the brain (ref. 25). The observations combined to suggest that these drugs exerted their actions on the brain by interfering with neurotransmitters.

The preceding information on aminergic neurotransmitters with proposed theories of activation and inactivation are demonstrated in Appendix B. This is not obvious from the program, and it is necessary to have the interaction of the student at the terminal to make one of several responses to which the "program logic" (fig. 7), will then make a judgement and continue to next part of return to the questions for another attempt for the correct answer. See Chapter II on TUTOR.

CHAPTER IV

TRANSMITTERS IN THE CNS

There is great current interest in drugs that modify human behavior. These drugs include psychotomimetic agents, drugs that produce hallucinations and other manifestations of the psychoses; tranquilizers, drugs that allay anxiety; and psychic energizers, antidepressant drugs that elevate mood and increase interest and drive. Many of these drugs appear to act by modifying transmission at synaptic junctions in the brain, and their discovery has stimulated great interest in the nature and properties of the transmitter agents involved.

Uneven distribution of a given substance throughout the CNS and a similar distribution of the enzymes responsible for the substance's synthesis and degredation suggest a transmitter role. A change in behavior coincident with a drug-induced change is also indirect evidence that the substance is a transmitter. More direct evidence is provided by differential centrifugation of brain tissue, which has demonstrated the presence of a number of suspected mediators in fractions known to contain nerve endings. Chemicals found in nerve ending fractions in the CNS include acetylcholine, norepinephrine, dopamine, serotonin, and prostaglandins. Additional evidence is provided by histochemical localization, which is now available for acetylcholine, norepinephrine, serotonin, and dopamine, see Chapter IV. It has also been shown that certain suspected mediators are liberated from the brain in vitro, and that acetylcholine and some other suspected CNS mediators excite single neurons when applied to their membranes by means of a micropipette

(microelectrophoresis). The substances currently known or suspected of being released from nerve endings are summarized in Table 2.

Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) is present in high concentrations in blood platelets and in the enterochromaffin cells of the gastrointentinal tract, and in the myenteric plexus. Lesser amounts are found in the brain, particularly in the hypothalamus (Table 3). Serotonin is found in relatively high concentrations in the lateral gray horns of the spinal cord, the raphe nuclei of the brain stem, the suprachiasmatic nuclei of the hypothalamus, and the olfactory tubecules.

Serotonin is formed in the body by hydroxylation and decarboxylation of the essential amino acid tryptophan (Fig. 20). It is inactivated principally by monoamine oxidase (Fig. 21) to form 5-hydroxyindoleacetic acid (5HIAA). This substance is the principal urinary metabolite of serotonin, and the urnary output of 5HIAA is used as an index of the rate of serotonin metabolism in the body.

The psychotomimetic agent, lysergic acid diethylamide (LSD) is a serotonin antagonist. The transient hallucinations and other mental aberrations produced by this drug were discovered when Dr. Albert Hofmann, the chemist who synthesized it, ingested some by accident. Although the relation of LSD to brain serotonin remains unsettled, its discovery called attention to the correlation between behavior and variation in brain serotonin content. Several substances which, like serotonin, are derivatives of tryptamine have psychotomimetic actions; psilocybin, a hallucinogenic agent found in certain mushrooms, is the best known of these compounds. The tranquilizing drug reserpine causes a pronounced depletion of serotonin from body stores, including the brain;

and it is difficult to decide which of its effects are due to serotonin depletion and which to catecholamine depletion. Monoamine oxidase inhibitors, which are psychic energizers, increase brain serotonin, but they also increase brain norepinephrine and dopamine. It has recently been possible to produce a selective depletion of brain serotonin by administering p-chlorophenylalanine, a compound that blocks conversion of tryptophan to 5-hydroxytryptophan. This is the rate-limiting step in serotonin biosyntheses (fig. 20).

Norepinephrine

The distribution of norepinephrine in the brain parellels that of serotonin (Tables 2 & 3). Large amounts are also found in the pineal gland (ref. 44). In the hypothalamus, nerve endings containing norepinephrine are plentiful around the neurons of the supraoptic and paraventricular nuclei. Endings are also plentiful in the dorsomedial, periventricular, suprachiasmatic, and arcuate nuclei. The biosynthesis and metabolism of norepinephrine and epinphrine are shown in Figure 13a, 14 & 15.

Evidence has now accumulated that the norepinephrine in the brain is related to mental function. It has been known for sometime that treatment with reserpine may cause depression and that monoamine oxidase inhibitors are psychic energizers (ref. 11). These drugs affect brain serotonin as well as brain catecholamines, but recent research with compounds that affect norepinephrine selectively indicates that mood is related to the amount of free norepinephrine available to synapses in the brain. When too little norepinephrine is available, depression results; and drugs such as monoamine oxidase inhibitors and amphetamine, which increase free norepinephrine, elevate mood. The tricyclic antidepressant such as desipramine appear to act in the same way; they decrease the re-uptake

of liberated norapinephrine, thus leaving more available to act on the postsynaptic structures.

The norepinephrine-containing endings in the hypothalamus also appear to be involved in the regulation of gonadotropin secretion and to inhibit the secretion of vasopressin and, possibly, oxytocin. There is some evidence that norepinephrine is involved in the control of food intake and, along with serotonin, in the regulation of body temperature. An inhibitory effect on autonomic discharge from the spinal cord has also been suggested.

There are small amounts of epinephrine and appreciable quantities of tyramine in the CNS, but no function has been assigned to these chemicals.

Dopamine

Dopamine is the immediate precursor of norepinephrine (Fig. 13a). The distribution of dopamine in the brain generally parallels that of norepinephrine; however, in the caudate and putamen, the concentration of norepinephrine is low and that of dopamine is very high (Table 1.). These nuclei contain most of the enzymes found in parts of the brain that are rich in norepinephrine, but their dopamine-β-hydroxylase activity is low. This is the enzyme that catalyzes the conversion of dopamine to norepinephrine; consequently, catecholamine synthesis stops at dopamine. Dopaminergic neurons whose cell bodies are in the substantia nigra end in the caudate nucleus and putamen . Others interconnect the limbic system with the interpeduncular nucleus. Dopamine is also found in high concentration in nerve endings in the median eminence of the hypothalamus. The cell bodies of the neurons ending in the median eminence are located for the most part in the arcuate nucleus.

Dopamine is inactivated by monoamine oxidase and by catechol-o-methyltransferase activation of norepinephrine (Figs. 15 and 16).

Evidence is accumulating that dopamine is related in some way to motor function. In parkinson's disease, the dopamine content of the caudate nucleus and putamen is about 50% of normal. Hypothalamic norepinephrine is also reduced, but not to so great a degree. Several drugs that produce parkinsonism-like states as undesirable side effects have been shown to alter the metabolism of dopamine in the brain. There is some evidence that dopamine facilitates conditioned avoidance reflexes. The hallucinogen mescaline is a derivative of dopamine. The dopaminergic neurons in the hypothalamus seem to play a role in the control of prolactic secretion and possible in the secretion of other anterior pituitary hormones as well.

Acetylcholine

Acetylcholine is distributed throughout the CNS with the highest concentrations in the motor cortex and the thalamus (Tables 1 and 3). The distribution of choline acetylase and acetylcholinesterase parallels that of acetylcholine. Most of the acetylocholinesterase is in neurons, but some is also found in glia.

Acetylcholine has been linked directly or indirectly to a variety of brain functions. A number of hallucinogenic agents are derivatives of atropine, a drug which blocks the effects of acetylcholine at post-ganglionic nerve endings. In male and female cats, the choline acetylase content of the hypothalamus is said the increase following castration, and in intact females it is reported to be high during diestrus and low during estrus. Injections of acetylcholine into the hypothalamus and

parts of the limbic system cause drinking. Application of acetylcholine to the supraoptic nucleus in dogs causes increased secretion of vasopression. In blinded rats, cholinesterase activity is decreased in the superior colluculi and elevated in the occipital cortex. Cortical levels of acetylcholine and cholinesterase are correlated with intelligence and behavioral characteristics in rats, although the significance of this type of correlation is uncertain. The interaction of acetylcholine and acetylcholinesterase is shown in Figures 10 & 11.

Histamine

There are large amounts of histamine in the anterior and posterior lobes of the pituitary and in the adjacent median eminence of the hypothalamus. The heparin-containing tissue cells called mast cells have a high histamine content, and most of the histamine in the posterior pituitary is in mast cells. However, the histamine in the anterior pituitary and the hypothalamus is not in mast cells. In other parts of the brain, the histamine content is very low. Histamine is formed by decarboxylation of the amine acid histidine (Fig. 19). In the brain, it is converted to methylhistamine; outside the brain, to imidazoleacetic acid. The latter reaction requires the enzyme diamine oxidase (histaminase) rather than monoamine oxidase, even though monoamine oxidase catalyzes the oxidation of methylhistamine to methylimidazoleacacetic acid. Fig. 16 illustrates the synthesis and catabolism of histamine.

So far, there is relatively little evidence other than uneven distribution to suggest that histamine is a synaptic mediator in the brain. However, the histamine content of the brain is increased by the tremor-producing drug, tremorine; by the psychotomimetic agent, mescaline; and by the transquilizer, (chlorpromazine). The brain content of histamine is decreased by reserpine.

Substance P

Substance P is a basic polypeptide which has a molecular weight of 1600. It apparently contains 13 amino acids, but its exact structure has not been established. It is found in appreciable quantities in the intestine, where it may be a chemical mediator in the myenteric reflex. In the nervous system, high concentrations are found in the hypothalamus and the dorsal roots of the spinal nerves, and there are particularly large amounts in the substantia nigra (Tables 2 and 3). Little is known about the anabolism and catabolism of this polypeptide, although brain tissue apparently contains enzymes that are concerned with its metabolism. Injections intramuscularly IM, of Substance P alter potentials associated with transmission in the sensory pathways in the spinal cord.

Prostaglandins

Prostaglandins--fatty acid derivatives found in high concentration in semen--are also found in the brain. They have been shown to be present in nerve ending fractions of brain homogenatea and to be released from the cortex, the cerebellum, and the spinal cord. When administered by microelectrophoresis onto nerve cell membranes, they alter the firing rates of the neurons. This suggests that they are synaptic mediators, but their definitive role remains to be determined.

Gamma-Aminobytric Acid

Although it was once thought that gamma-aminobytric acid (GABA) was the chemical mediator released by the interneurons responsible for postsynaptic inhibition in the spinal cord, this now seems unlikely. It may play a role in presynaptic inhibition, but its relation to this phenomenon is uncertain. In the brain (Table 1), it decreased exitatory activity but is apparently not a synaptic mediator. There is an increase

in the amount of GABA released from the brain when the EEG pattern is that of slow wave sleep.

GABA is formed by decarboxylation of glutamic acid. Glutamic acid depolarizes neurons when placed directly on their membranes by microelectrophoresis, and could be a transmitter agent itself. GABA can reenter the citric acid cycle by conversion to succinic acid (Fig. 22). The citric acid cycle is the major pathway by which intermediates formed in the catabolism of carbohydrates, proteins, and fats are metabolized to CO_2 and H_2O. Pyridoxal phosphate, a derivative of the B complex vitamin, pyridoxine, is a cofactor for the enzyme that catalyzes the formation of GABA from glutamic acid. The transaminases responsible for the formation of glutamic acid and for the formation of succinic semialdyhyde are also pyridoxine-dependent; but, unlike the transaminiation, the decarboxylation is essentially irreversible. Consequently, the GABA content of the brain is reduced in pyridoxine deficiency. Pyridoxine deficiency is associated with signs of neural hyperexcitability and convulsions, although pyridoxine treatment is unfortunately of no value in most clinical cases of iodiopathic epilepsy.

The preceding information on transmitters in the CNS is demonstrated in Appendix C, as it has been programmed into a PLATO IV computer using TUTOR language.

CHAPTER VI

PSYCHO-PHARMACOLOGICAL DRUGS

Since the introduction of antipsychotic drugs in 1954, it seemed reasonable to expect that depression might also by influenced by more selective drugs than the previously employed psychomotor stimulants such as amphetamine. The inhibitors of monoamine oxidase (MAO) were soon introduced for this purpose. More recently, a group of dibenzazepine compounds such as impiramine (Tofranil), amitriptyline (Elavil), and their derivatives have been widely used as antidepressants.

In addition to these newer antidepressant drugs, some of the older psychomotor stimulants such as amphetamines are still used in management of depression.

The antipsychotic agents include the phenothiazines, butyrophenones, thioxanthenes and reserpines. The mood-active drugs include the tricyclics, the monoamine oxidase inhibitors and the amphetamine stimulants.

The nonbarbiturate minor tranquilizers and sedatives include Diazepam, Meprobamate and oxazepam. The nonoarbiturate hypnotics include Glutethimide, Ethchlorvynol and Methprylon. A more complete glossary of drugs with generic name, brand name and manufacturer is shown in the table in Appendix A.

Tranquilizing drugs differ from the hypnotics with respect to selective action on behavior; antidepressants differ from the psychomotor stimulants by preferential effect on mood and behavior. The drug of choice being related to its structure, length of side chain and type of groups on code chains which can alter the sedative effect,

antipsychotic effect, antihistamine effect and various side effects. Some of these drugs are of intrest in the treatment of depressive states. The psychotomimetic drugs are experimental tools in reduction of toxic psychosis. Since Neuroleptic (antipsychotic) drugs are distinct from tranquilizer (such as meprobamate and diazepam) antidepressants (such as imipramine and amitriptyline) and other groups of psychotropic dugs, they may be divided into three subcategories on the basis of chemical structure (a, b) or mechanism of action (c):

(a) phenothiazines and thioxanthenes: chlorpromazine, thrioridazine, fluphenazine, chlopenthixol, Appendix A.

(b) butyrophenones: haloperidol, trifluperidol, fluspirilene pimozide, Appendix A.

(c) reserpine and related compounds: Tetrabenazine, benzquinamide.

Antidepressant drugs have effects similar to Cocaine which is a potent stimulant that can produce psychosis and also intensifies the action of noradrenaline. When radioactive noradrenaline is injected into cats that have been given cocaine, the uptake of catecholamines by the sympathetic nerves is prevented, demonstrating that cocaine magnifies the effect of noradrenaline by preventing its capture and inactivation and leaving larger amounts of the catecholamine to react with the effector cell. Antidepressant drugs such as impiramine have the same effect: they block the uptake of noradrenaline into sympathetic nerves. By using radioactive noradrenaline amphetamine, which is both a stimulant and a mind-altering drug, affects noradrenergic nerves in two ways: it blocks the uptake of noradrenaline and also promotes the release of the neurotransmitter from nerves.

Many drugs that are effective in the treatment of hypertension affect the storage and release of noradrenergic transmitters. Reserpine and guanethedine reduce blood pressure by preventing the nerves that raise the pressure from storing noradrenaline. Antihypertensive drugs such as alpha methyl dopa, on the other hand, are transformed by enzymes in the nerve into substances that resemble the noradrenaline chemically. The "false transmitters" are stored and released along with natural neurotransmitters, diluting them and thus reducing their effect.

Some of the drugs that relieve mental depression also interfere with the uptake, storage, release or metabolism of noradrenaline. Imipramine blocks the uptake of noradrenaline by nerves and amphetamine both releases noradrenaline and blocks its uptake, monoamine oxidase inhibitors, as their name implies, prevent the metabolism of the catecholamine. In other words, all these antidepressants produce similar results by different mechanisms: they increase the amount of catecholamine in the synaptic cleft, with the result that more transmitter is available to stimulate the receptor (Fig. 25). Conversely, reserpine, a compound that decreases the amount of the chemical transmitters, sometimes produces depression. These considerations led to the proposal of a catecholamine hypothesis of depressive states, which holds that mental depression is associated with the decreased availability of brain catecholamine and is relieved by drugs that increase the amount of these transmitters at the adrenergic receptor. Although the hypothesis is not entirely substantiated, it has provided a valuable framework within which new approaches to understanding depression can be sought. See Chapter I V.

Neuroleptics or antipsychotic drugs such as chlorpromazine, haloperidol and reserpine have revolutionized the treatment of schizophrenia, dramatically reducing the stay of schizophrenics in mental hospitals and saving many billions of dollars in hospital care. Research in the past decade has shown that antipsychotic drugs also exert their effect on the catecholamine neurotransmitters. Carlsson (ref. 11) had observed that antischizophrenic drugs caused an increase in the formation of catecholamines in the rat brain, and he formed the hypothesis that this was owing to the drug's ability to block dopamine receptors. Work by other investigators has confirmed and extended this hypothesis. Antipsychotic drugs do block dopamine receptors in the brain, and there is a strong association between the blocking ability of various drugs and their capacity to relieve schizophrenic symptoms. These findings point clearly to the involvement of the dopaminergic nerves in schizophrenia.

Amphetamine has also helped to clarify the nature of schizophrenia. Taken repeatedly in large amounts, amphetamine produces a psychosis manifested by repetitive and compulsive behavior and hallucinogenic delusions that are indistinguishable from the symptoms exhibited by paranoid schizophrenics. Amphetamine released catecholamines from nerves in the brain to stimulate both noradrenergic and dopamine receptors. After doing experiments with two forms of amphetamine, Solomon H. Snyder of the Johns Hopkins University Medical School hypothesized that the schizophrenia-like psychosis the drug produces is due to excessive release of dopamine. The ability of antischizophrenia drugs, which block dopamine receptors, to relieve symptoms of amphetamine psychosis is consistent with this hypothesis.

Although there have been rapid advances in our knowledge of neurotransmitters in the past 20 years, much remains to be discovered about these compounds. Only a few of the chamical transmitters of the brain neurons have even been characterized. The role of neurotransmitters in behavior, mood, reproduction and learning and in diseases such as depression, schizophrenia, motor disorders and hypertension is beginning to evolve. If only the present trend toward reducing the funds committed to research support can be reversed, exciting new discoveries about neurotransmitters should soon be made, many of which will surely contribute directly toward the treatment or cure of some of man's most tragic afflictions.

Antidepressants--Hydrazine MAO Inhibitors

Starting with iproniazid (Marsilid) , a variety of monoamine oxidase inhibitors have been introduced for treatment of depressive states and for certain other therapeutic purposes. Despite the great popularity of these drugs, it should be kept in mind that they are potentially dangerous medications. The exact functions of the enzyme monoamine oxidase in the body are not understood with certainty and the consequences of its prolonged inhibition may not be completely known.

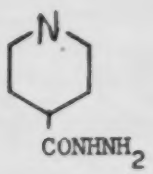
Among the many disadvantages of the hydrazine MAO inhibitors the following may be listed: slow action, hepatotoxicity, over-stimulation, postural hypotension, insomnia, constipation, weight gain, and paradoxical behavior. Because of these disadvantages, they are being replaced by non-hydrazine MAO inhibitors and suppressant drugs.

The pharmacology of iproniazid is discussed because of its theoretical interest. The drug is no longer available, having been withdrawn because

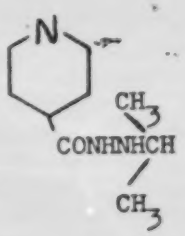
of hepatotoxicity. Imipramine now is the most widely used antidepressant.

Development of Monoamine Oxidase Inhibitors

Iproniazid (Marsilid) was synthesized in 1951 as a chemotherapeutic agent for tuberculosis. It is isopropyl derivative of isoniazid (Rimifon), which was previously shown to be a highly potent inhibitor of the growth of the tubercle bacillus. The structural formulas of iproniazid and isoniazid appear below.



Isoniazid
(Isonicotinic acid hydrazide)



Iproniazid
(1-isonicotinyl-2-isopropylhydrazine)

The combined antidepressant and enzyme-inhibitory actions of iproniazid stimulated a great deal of interest in similar compounds. A large variety of basically similar drugs are being used at the present time for various therapeutic purposes.

Effects of Iproniazid in Man and Animals

The effect of iproniazid in man depend on the dosage and the length of time during which the drug is administered. As with many other psychopharmacologic agents the preexisting personality of the patient has much to do with the kind of response which is obtained.

Many of these effects can be seen also in animal experiments. In large doses iproniazid can produce hyperactivity in dogs (reference 47)

and some muscle twitchings were observed on chronic administration of the drug. The central nervous system stimulant actions of iproniazid are shown particularly well wher the drug is administered prior to reserpine (Table 4). Under these conditions iproniazid cannot only prevent the depression caused by reserpine but can also produce marked excitement and even convulsions. See Fig. 11.

It was at first surprising to find that this psychic stimulant not only failed to antagonize the action of the babiturates but also actually prolonged their effect. It was shown, however, that this potentiating action on the barbiturates is due to interference with the metabolism of barbiturated by inhibition of microsonal enzymes in the liver (reference 18). Some of the newer monoamine oxidase inhibitors do not have this inhibitory enzyme action, and this fact is used as suggestive evidence for their lesser hepatotoxicity.

Mode of Action of Iproniazid

Since the drug inhibits monoamine oxidase and also has important neuropharmacologic effects, the basic question is the possible relationship between these two phenomena.

It is conceivable that enzyme inhibiting actions of iproniazid have nothing to do with its antidepressant action. This view has received some support from the fact that the recently introduced antidepressant imipramine (Tofranil) has effects similar to those of iproniazid on behavior but is not an inhibitor of monoamine oxidase. While imipramine and related antidepressant do not inhibit monoamine oxidase, they block uptake of norepinephrine by neural tissues (reference 46), a drug effect sometimes referred to as cocaine-like. Still, there is

some suggestive evidence that a relationship exists between the pharmacologic effects of the monoamine oxidase inhibitors and their influence on amine metabolism.

The enzyme monoamine oxidase is widely ditributed in the body. Histochemical studies show its presence in practically all tissues. Its function may be the oxidative deamination of such compounds as serotonin, tyramine and dopamine, since the potency of these amines is greater in animals pretreated with the inhibitors of monoamine oxidase. This role is still speculative, however.

At one time, it also was believed that norepinephrine and epinephrine are metabolized by monamine oxidase. The studies of Axelrod discussed previously clearly show, however, that injected catecholamines are metabolized by the catechol-O-methyl transferase enzyme. This finding fits well with the previously demonstrated lack of potentiation of norepinephrine or epinephrine by iproniziad. It is nevertheless interesting that the monoamine oxidase inhibitors can cause elevation in the norepinephrine content of the brain. It has been suggested (by B.B. Brodie, ref. 10) that the central stimulatory activity of the monoamine oxidase inhibitors may be related to the influence of these drugs on brain norapinephrine concentrations.

There are several points in favor of the idea that the monoamine oxidase inhibitors exert their pharmacologic effects as a consequence of enzyme inhibition and the accumulation of various amines. First of all, the onset of action of these compounds is slow. It may take from four to twenty days for their antidepressant action to become manifest. With some of the more potent compounds, the onset of action may be only twelve to twenty-four hours. In animal experiments it has been shown

that the effect of these drugs is better correlated with the degree of enzyme inhibition than with the presence of the drugs in the body (reference 23). It is important also that when the administration of the monoamine oxidase inhibitors is discontinued their antidepressant effects may persist for several days.

Comparison of Newer Monoamine Oxidase Inhibitors with Iproniazid

A number of newer nomoamine oxidase inhibitors have been introduced into therapeutics. The most important ones are phenelzine (Nardil), nialamide (Niamid), and isocarboxazid (Marplan).

These various drugs differ from each other in effectiveness in the incidence of toxic effects following their use, and in the manner in which they are metabolized in the body.

The recommended usual daily dose of these drugs (Table 5) reflects their varying effectiveness.

It has been suggested (reference 41) that a scientific approach to dosage would be the determination of the effect of the various drugs on urinary tryptamine excretion in man, since monoamine oxidase inhibitors cause a marked increase in the urinary excretion of this amine.

Although it is believed that the newer monoamine oxidase inhibitors are relatively less toxic than iproniazid in animal experiments and in clinical trials, it should be emphasized that they are capable of causing serious toxic manifestations.

In a clinical trial on 2000 patients it is stated (reference 36) that overdosage with these drugs caused the following side effects: postural hypotension, constipation, urinary hesitancey, blurring vision, vertigo, nausea, and anorexia. Acute liver damage was observed in four

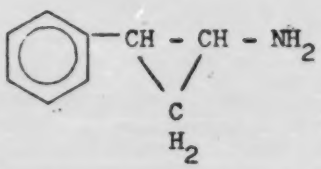
patients, but other factors may have contributed to the hepatic damage. Anemia developed in 6% or the patients, leukopenia occurred in a few, and an itching maculopapular rash was found in 1% of those treated.

Transient elevation of serum transaminase has also been observed in a number of patients, but it disappeared within a few weeks when medication was discontinued.

Nonhydrazine MAO Inhibitors--Tranylcypromine (Parnate)

Tranylcypromine (Parnate) is a potent nonhydrazine MAO inhibitor which also has a stimulant action similar to amphetamine. Thus, it is a bimodal antidepressant.

The drug is closely related to the amphetamines.



Tranylcypromine (Parnate)

Tranylcypromine provides fast, direct stimulation similar to amphetamine, but its action sustained probably as a consequence of its MAO inhibitory action. Its fast action is an advantage over the hydrazine drugs, but it shares with the latter the ability to cause postural hypotension.

Severe hypertensive reactions have occurred in patients treated with tranylcypromine following the ingestion of aged cheese (reference 26). These reactions may be attributed to the presence of tyramine and other monoamines which would normally be detoxified by monoamine oxidase. Bacause of these reactions, the drug was temporarily withdrawn from the market.

For treating depressive reactions, tranylcypromine is administered orally, 1 mg. twice a day for several weeks.

Pargyline is discussed with the antihypertensive drugs.

Clinical uses of Monoamine Oxidase Inhibitors

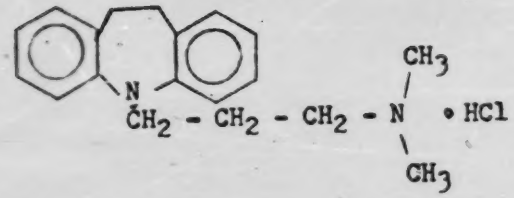
The major use of the monoamine oxidase inhibitors is for their antidepressant action. Good results are claimed in a variety of depressive syndromes.

These drugs have been recommended for certain other purposes. It is claimed that the monoamine oxidase inhibitors may have a beneficial effect in angina patients (reference 21). The mode of action of these drugs in angina is still mysterious, and some investigators feel that there is really no objective evidence to indicate that they improve coronary blood flow. If the drugs act mainly on the initiation or perception of pain in angina, their ultimate effect on survival may not be favorable since they may promote excessive activity in patients whose coronary blood flow is deficient.

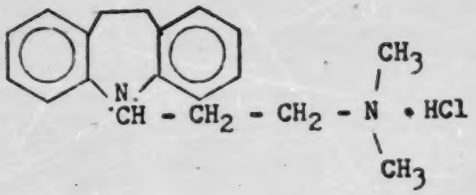
Severe hypertensive reaction may occur in patients being treated with any monoamine oxidase inhibitor following ingestion of cheese and other fermented foods or beverages and following administration of a variety of drugs, particularly indirectly acting sympathomimetics.

Antidepressants which are not MAO Inhibitors

The suppressant drugs used as antidepressants, imipramine (Tofranil), and amitriptyline (Elavil), and their desmethyl derivatives, are chemically similar to the phenothiazines. Their pharmacologic properties are also similar, but empirically they have been found useful as antidepressants. Imipramine is now one of the most widely used antidepressant.



Imipramine (Tofranil) hydrochloride



Amitriptyline (Elavil) hydrochloride

Many of the toxic effects of these drugs are similar to those caused by the phenothiazines. Serious reactions include blood dyscrasias and jaundice. Less serious reactions are postural hypotension, dryness of the mouth, constipation, tachycardia, blurring of vision, mild parkinsonian syndrome, increased perspiration, nausea, and drowsiness or insomnia. Although the incidence of blood dyscrasias and jaundice are less common than with the phenothiazines, these hazards should be taken into consideration before these drugs are prescribed for minor illnesses.

The basic pharmacology of imipramine and amitriptyline is quite complex. These drugs do not inhibit monoamine oxidase, but do have anticholinergic, antiserotonin, and antihistaminic actions. In fact, amitriptyline is a potent antihistaminic. The basic mechanism of their antidepressant action may be related to the fact that imipramine can block the uptake of norepinephrine by brain and other organs (references 3, 14, 46).

Imipramine also has a cocaine-like effect on uptake and binding of injected norepinephrine in vivo. It would be possible to speculate that the common denominator between the actions of the monoamine oxidase inhibitors and imipramine is the presence of elevated free norepinephrine levels in the brain.

Both the MAO inhibitors and the antidepressants which are not MAO inhibitors protect animals against the depressant effects of reserpine. MAO inhibitors prevent brain catecholamine depletion ordinarily induced by reserpine. Imipramine and related drugs may antagonize the effects of reserpine by blocking the uptake of norepinephrine released within the brain.

In an interesting case of imipramine poisoning, the patient had severe hypotension, convulsions, apnea, cardiac arrest, oliguria, and hyperpyrexia. Treatment consisted of assisted respiration, barbiturates to control the convulsions, gastric lavage, and vasopressor agents. Dialysis was also used, and mannitol proved to be an effective osmotic diuretic (reference 22).

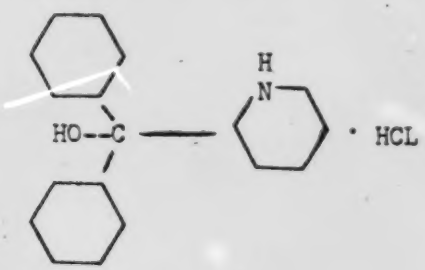
Toxicity of Combination of Antidepressants

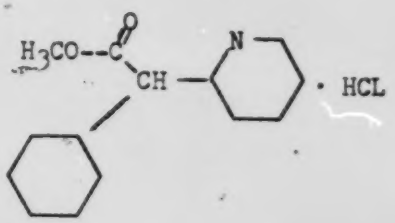
It is unwise and dangerous to combine some of the antidepressant medications. The simultaneous administration of MAO inhibitors and amitriptyline or imipramine may produce severe atropine-like reactions with tremors, hyperpyrexia, and convulsions (reference 24). A one-week interval is recommended between the time an MAO inhibitor is discontinued and a suppressant antidepressant is administered.

Psychomotor Stimulants

Amphetamine has been used for years as a mood elevator in

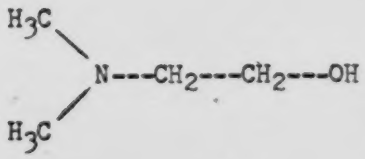
depressed patients. Its disadvantages are its cardiovascular effect and the letdown which follows the short period of stimulation. Some mild stimulants, probably related in action and chemistry to amphetamine, are sometimes used in depressive states. These are pipradrol (Meratran) hydrochloride and methylphenidate (Ritalin) hydrochloride. Pipradrol, in doses of 1 or 2 mg., may elevate mood and depress appetite. Methylphenidate, administered in 10 mg. doses three times a day, may act in a similar fasion, but more slowly.





Pipradrol (Meratran) hydrochloride

Methylphenidate (Ritalin) hydrochloride



acetamidobenzoate

Deanol (Deaner) acetamidobenzoate

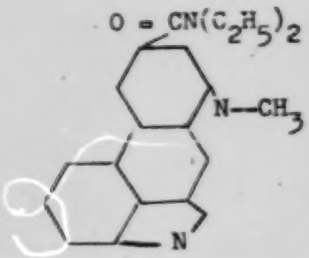
Deanol acetamidobenzoate (Deaner) has been introduced as a very mild stimulant on the basis of the theory that it may act as a precursor for acetylcholine in the brain. There is no unanimity of opinion for this explanation of its action. Its effects are so mild that some observers even question its usefulness, although there are some double-blind studies in children which show that improvement in alertness occurs after prolonged treatment. The drug is essentially useless in treatment of depression. Daily dosage is 10 to 50 mg. orally.

Psychotomimetic drugs

Certain drugs can produce toxic psychosis in small doses. Interest in these compounds has been great, partly because they have some usefulness in experimental psychiatry and partly because their actions suggest that perhaps there may be a chemical basis for mental illness. The various chemical theories of mental illness have been critically reviewed by Kety (ref. 25). The conclusion is that they are not proved.

Some of the most interesting psychotomimetic agents are lysergic acid diethylamide (LSD; Delysid), mescaline, and psilocybin.

Lysergic acid diethylamide is closely related to the ergot alkaloids. Its structural formula is as follows:

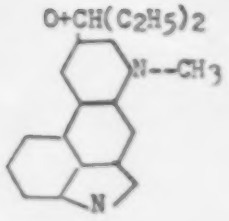


Lysergic acid diethylamide (LSD)

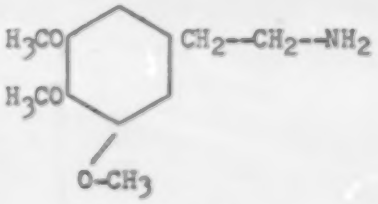
The discovery of its hallucinogenic properties was made by the chemist who synthesized the drug, who noted these reactions on himself. Subjects who take a few micrograms of LSD develop auditory and visual hallucinations. The body may feel distorted, the arms, for example, appearing to be at a great distance. The subject may become fearful and irrational.

In animal experiments, LSD may cause excitement and hyperthermia. Upon repeated administration, considerable tolerance develops to the drug.

Lysergic acid diethylamide is a potent antagonist of serotonin on smooth muscles. The association of this antiserotonin activity and the psychic effects suggested many interesting speculations concerning the role of serotonin in behavior. It should be remembered, however, that there is no evidence to indicate that the central actions of LSD are due to its antagonistic effect on serotonin. These actions may simply be a direct effect on an unusual amine. Brom-lysergic acid diethylamide has antiserotonin effects on smooth muscles similar to those of LSD, but the drug has no hallucinogenic properties. There is also no evidence for the normal occurrence of an LSD-like substance in mammals.



Lysergic acid diethylamide (LSD)



Mescaline

Mescaline is obtained from the cactus known as peyote or mescal (Lophophora williamsii) found in the southwestern region of the United States. This cactus is used by some Indians in religious ceremonies. Persons who have ingested dried peyote buttons report that they cause a stuporous state with unusual visual hallunications. Colored lights, which are reported to be extremely beautiful, are the most striking feature of these hallucinations. Interestingly, some volunteers report that they have seen colors which they did not know existed.

Mescaline, the active principle of peyote, is 3, 4, 5-trimethoxyphenethylamine, a structure resembling the sympathomimietic amines. The compound has some interest in experimental psychiatry.

Psilocybin (O-phosphoryl-4-hydroxy-N-dimethyl tryptamine) has been isolated from Mexican mushrooms which have hallucinogenic effects. Chemically, it is closely related to serotonin. It is of great interest that compounds related to the endogenously occurring amines have hallucinogenic properties.

The information about some of the drugs which effect the transmitter chemicals and in the several methods of potentiating and/or interfering with these chemicals (Fig. 25 & 26) are demonstrated in Appendix B. Appendix B is written in TUTOR language and programmed into the PLATO IV computer system.

Appendix B, C, & D are reproduced exactly as seen on the plasma panel by means of a Xerox copier attached to the terminal. The PLATO lesson and section on TUTOR language are intended to clarify these appendices.

SUMMARY AND CONCLUSIONS

There are several reasons for undertaking this study. One is to determine which of the available Computer-Assisted Instruction (CAI) or Computer-Assisted Education (CAE) programs suit this effort and then present some example lessons. The work of D.L. Bitzer and associates, in their presentation at UNESCO, Paris, France 1972 (ref. 7) indicates interest in the progress and value to the field of education for this type of Education Assistance to utilize the concept of "Biogenic Amines" as synaptic neurotransmitters, and in Chapters IV and V how some drugs effect this transmission. Another is to show a method of presenting a problem, with its teaching strategy, the possibilities of various branching conditions and eventually how these can be solved. The solutions can vary, displaying successful or unsuccessful treatment for either the student or the patient. This is not time consuming, due to the speed of the computer, or it is not fatal because the patient is simulated (Appendix D).

For many years, the only substances considered as transmitters for the Central Nervous System (CNS) were acetylcholine and norepinephrine (noradrenaline). In the past decade, this list has grown rapidly to include a wide range of naturally occuring amino acids, peptides and other biogenic amines such as dopamine, 5-hydroxytryptamine, (5-HT) and histamine. Further, new studies indicate the action of transmitter substances to be specific for separate receptors.

If the premise of P.E. Bloom (ref. 9) is followed, thoughts can be expressed less in the terms of a biologist or a psycho-

pharmacologist and more in the terms of a computer scientist. It is possible that a very complex neuronal "machine language" has evolved, not only to regulate the flow of information and reaction between certain sets of neurons, but to supply them with the mechanisms for recognizing the origin of the impulses, retaining or erasing the information and possibly modifying it before reacting to it. With this thought of "machine language" in mind, are the neurotransmitters one form of a vocabulary by which the instructional language of the brain directs addressing of information and reaction reflexes? We as educators need to be able to translate the chemical vocabulary offered by synaptic transmitters. I believe Computer-Assisted Education systems lends credibility to the above premise and practicality to teaching difficult subjects, a means of review for the student, resident physician and possibly the educator whenever necessary.

The problems in teaching psychopharmacology are surfacing in the recent study by Petti (ref. 33) who evaluated the training of second year psychiatric residents and medical students in a perspective study. The diagnosis and chart material of patients who received a diagnostic evaluation correlated poorly for almost fifty percent of the records made by students and for twenty-five percent made by the residents. Ten percent of the charts were so poor that they could not be used. The appropriate dosage and the correct medications were used only about one-half of the time by residents. There was significant evidence of polypharmacy.

In conclusion, the need for more intensive teaching methods in psychopharmacology to medical students and residents noted in the

above reference is in agreement with the discussions with several educators mentioned in Chapter I. This lends a timely and usable purpose for this study.[1]

1. The University of Illinois Medical Center has several educators who have expressed a desire to utilize Appendix B and C computer programs in their study programs. One educator intents to televise the animation for a class of 30 or more. Appendix D is to be utilized in Pharmacology section, which will involve a continuing upgrading as drug usage changes and new drugs are added (March 1975).

An additional note is the pending faculty Staff appointment.

Fig. 1 Map of a Medical Problem with Forced Branching

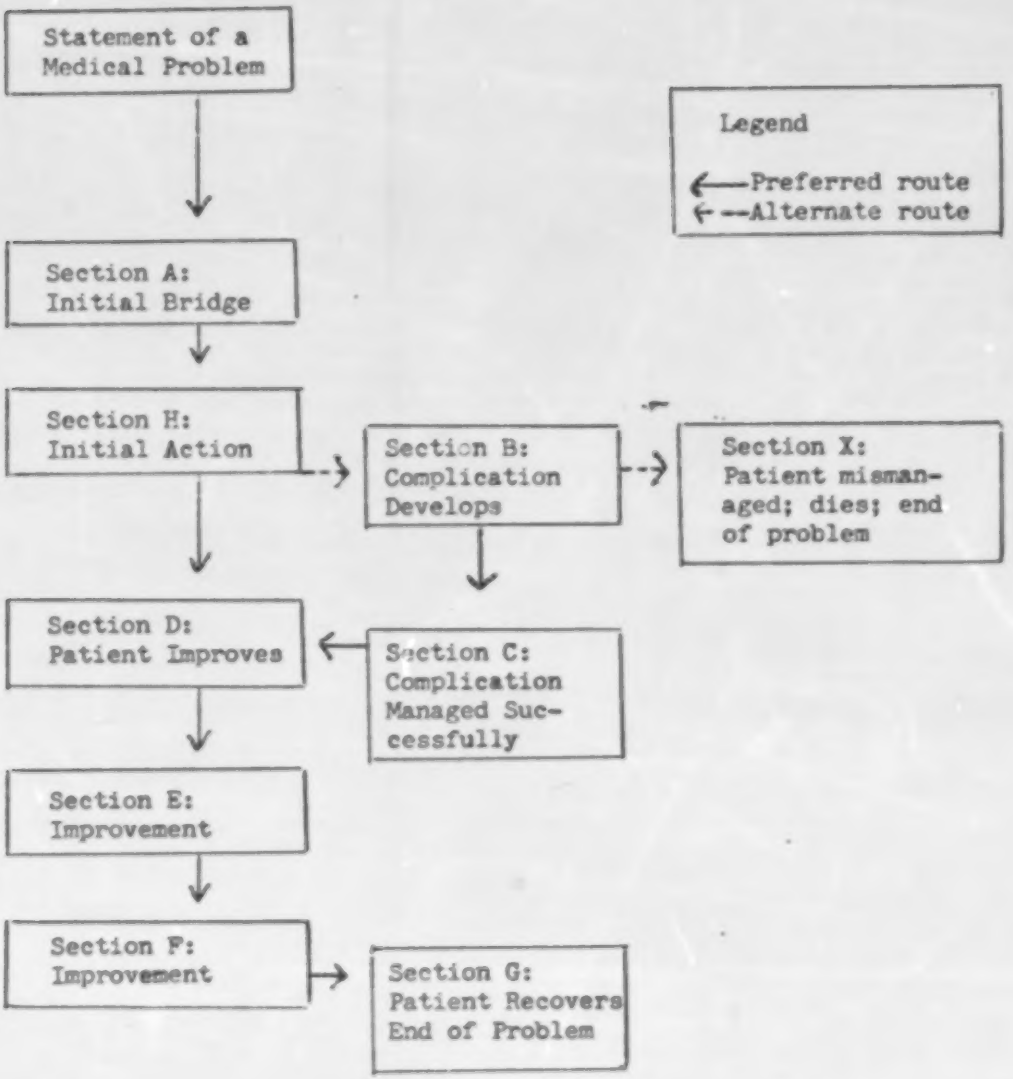

Statement of a Medical Problem
Legend
←—Preferred route
←--Alternate route
Section A: Initial Bridge
Section H: Initial Action
Section B: Complication Develops
Section X: Patient mismanaged; dies; end of problem
Section D: Patient Improves
Section C: Complication Managed Successfully
Section E: Improvement
Section F: Improvement
Section G: Patient Recovers End of Problem

Fig. 2.
OPENING SCENE

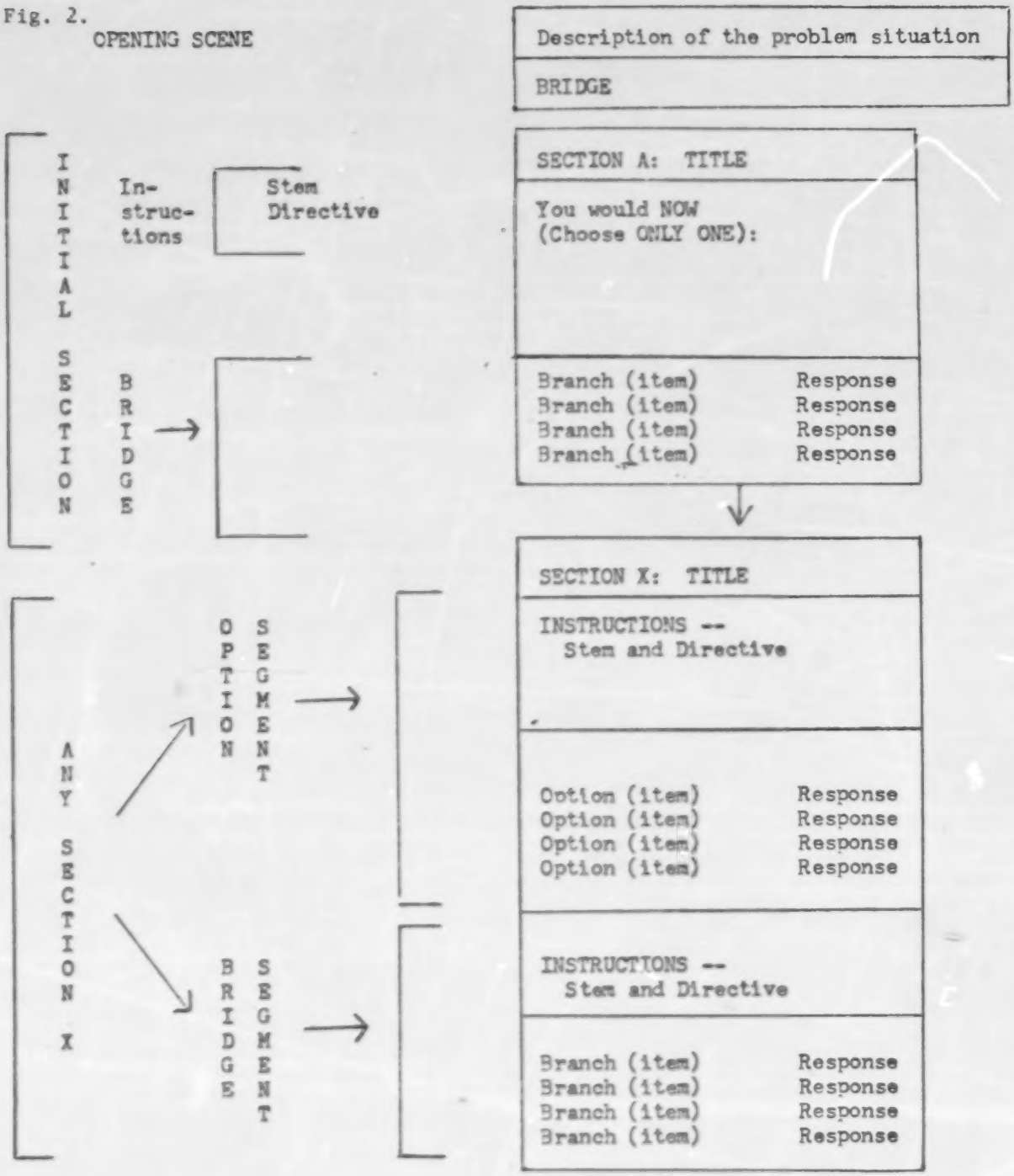


Fig. 3 SCORING FORMULAS

1. Proficiency (%)

The sum of (+) and (-) points for options chosen, divided by the maximum possible score, converted to percent.

$$P = \frac{\Sigma(+) + (-)}{\text{Max. Score}} \times 100$$

Example:

Examinee X made the following choices on a problem where 90 was maximum score.

No. of Choices	Weight	Sum
3	16	48
2	8	16
4	2	8
2	0	0
2	-1	-2
2	-4	-8

$$P = \frac{(72) \times (-10)}{(90)} \times 100$$

P = 68.8 or 69%

Fig. 4

2. Errors of Omission %

100% minus (the sum of the positive points chosen, divided by maximum possible score), converted to percent.

$$E.O.\% = (100) - \frac{\Sigma(+)}{\text{Max. Score}} \times 100$$

For the above examinee:

$$E.O. = 100 - \frac{72}{90} \times 100$$

E.O. = 20%

Fig. 5

3. Errors of Commission (%)

The sum of the negative points chosen, divided by maximum possible score, converted to percent.

$$E.C.\% = \frac{\Sigma(-)}{\text{Max. Score}} \times 100$$

For the above examinee:

$$E.C.\% = \frac{10}{90} \times 100$$

E.C.% = 11%

Note:
100% - E.O.% + E.C.% = %
100% - 20% + 11% = 69%

Fig. 6

4. Efficiency (%)

The number of positively weighted choices made, divided by the total number of choices made, converted to percent.

$$E\% = \frac{\text{No. of (+) choices}}{\text{No. of all choices}} \times 100$$

Example:

For the above examinee:

6 choices were +
2 choices were 0
4 choices were -
15

$$E = \frac{9}{15} \times 100$$

$$E = 60\%$$

Fig. 7

5. Competence Index (5)

The Proficiency index weighted by the Efficiency index.

$$C = \frac{(P \times E/100) + P}{2}$$

For the above examinee:

$$C = \frac{(69 \times 60/100 + 69}{2} = 55\%$$

Note: Any rational method of weighting proficiency and efficiency can be employed to yield a competence score.

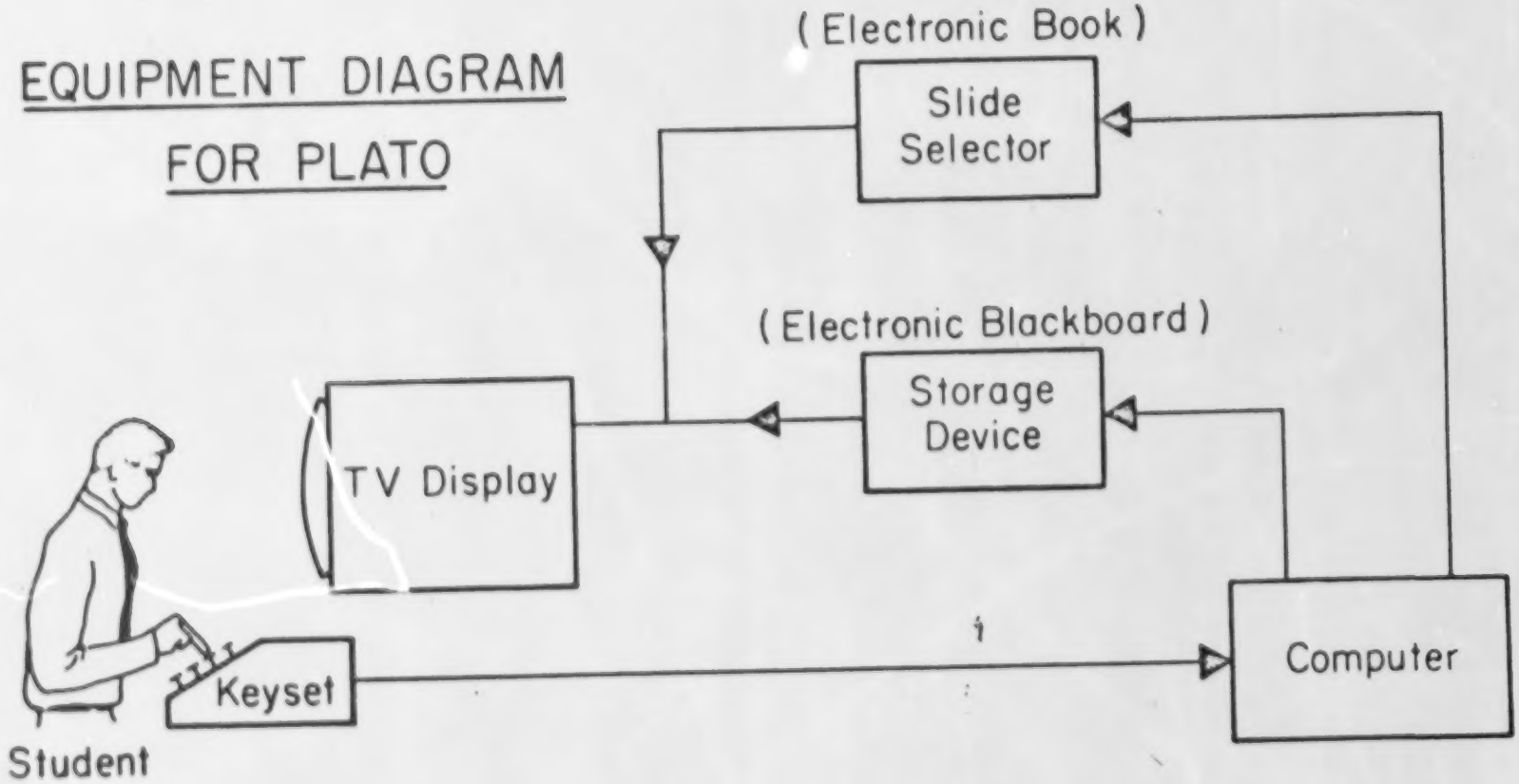

EQUIPMENT DIAGRAM
FOR PLATO
(Electronic Book)
Slide
Selector
(Electronic Blackboard)
Storage
Device
TV Display
Keyset
Student
Computer

FIG. 6

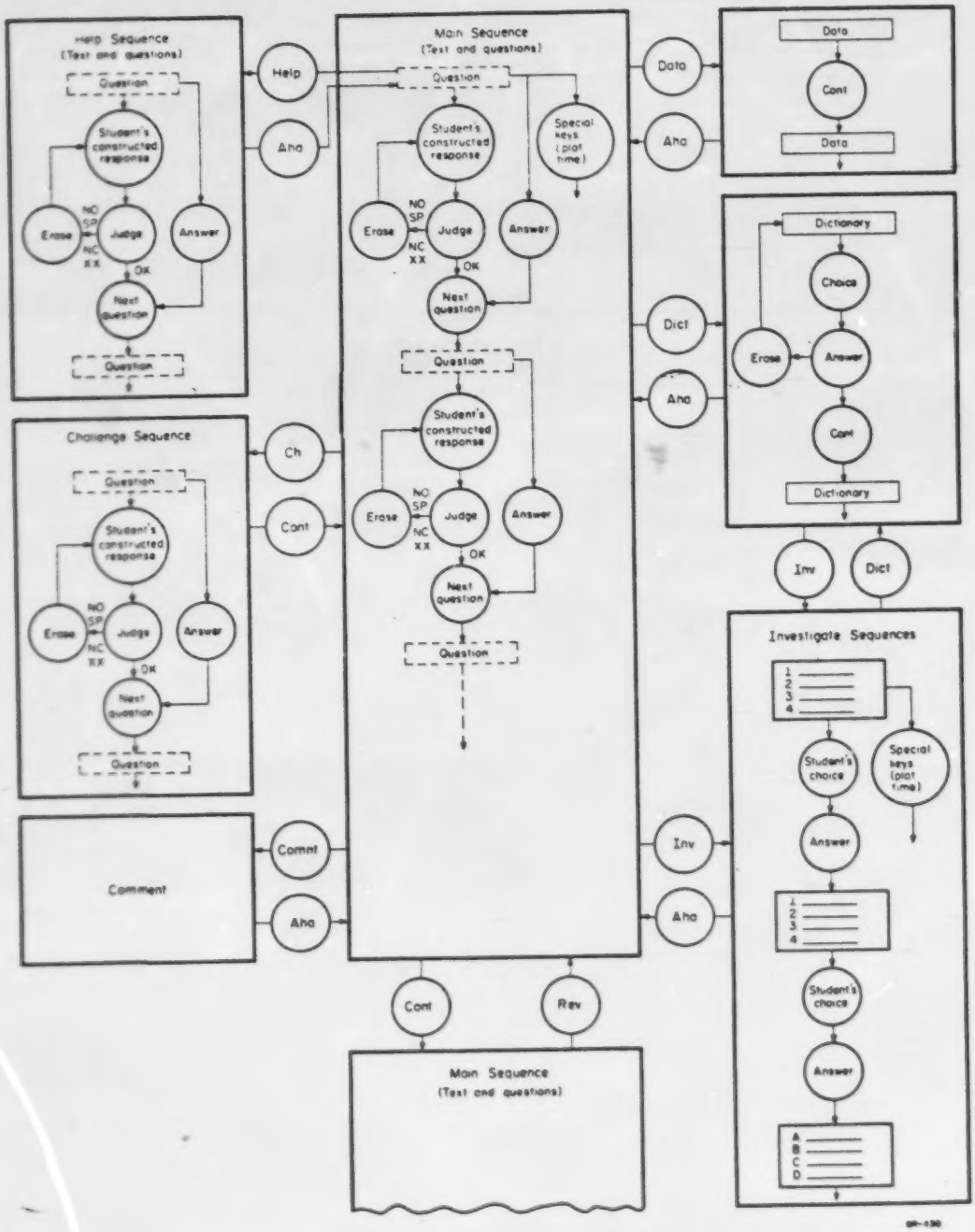

Help Sequence
(Text and questions)
Question
Student's constructed response
Erase
NO SP
NC XX
Judge
Answer
OK
Next question
Question
Help
Aha
Main Sequence
(Text and questions)
Question
Student's constructed response
Special keys (plot time)
Erase
NO SP
NC XX
Judge
Answer
OK
Next question
Question
Student's constructed response
Erase
NO SP
NC XX
Judge
Answer
OK
Next question
Question
Data
Aha
Data
Cont
Data
Dict
Aha
Dictionary
Choice
Erase
Answer
Cont
Dictionary
Inv
Dict
Challenge Sequence
Question
Student's constructed response
Erase
NO SP
NC XX
Judge
Answer
OK
Next question
Question
Ch
Cont
Comment
Comnt
Aha
Inv
Aha
Investigate Sequences
1
2
3
4
Student's choice
Special keys (plot time)
Answer
1
2
3
4
Student's choice
Answer
A
B
C
D
Cont
Rev
Main Sequence
(Text and questions)

Fig. 7

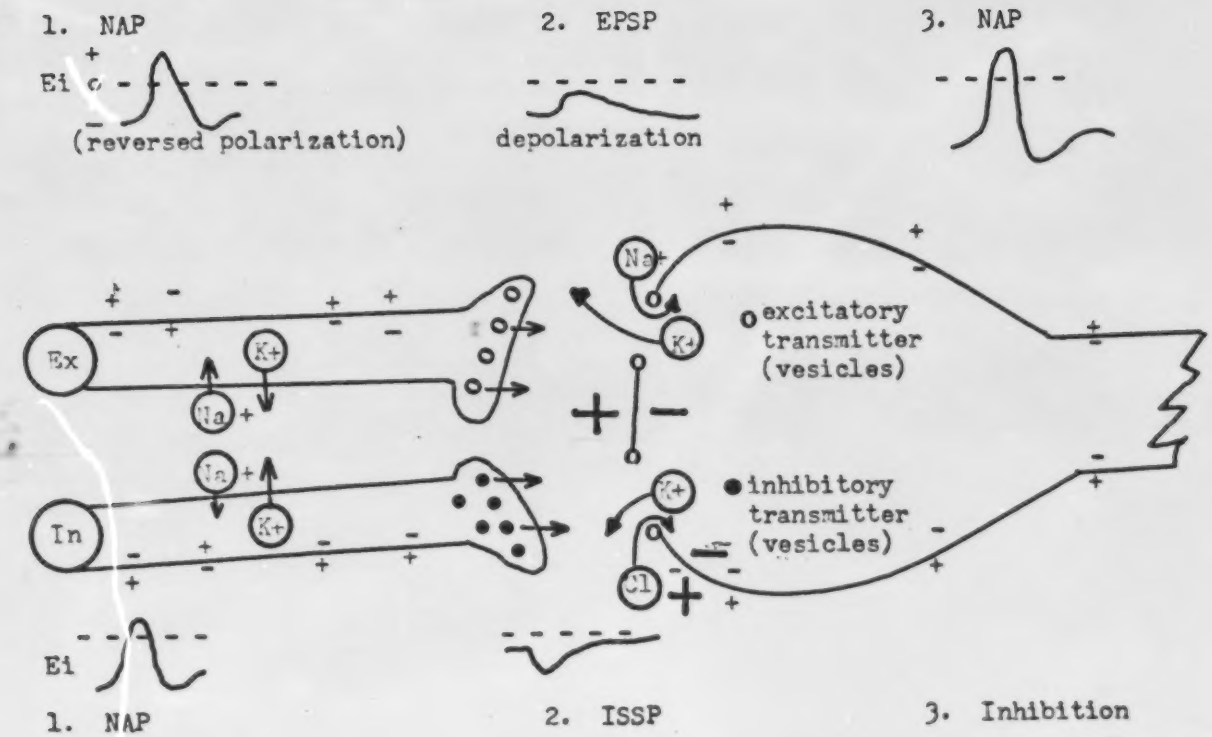


Fig. 8 1. The nerve action potential (NAP) consisting of a self-propogated reversal of negativity (the Ei internal potential goes from a negative value through zero potential, indicated by a broken line, to a positive value) of the axonal membrane, arrives at the presynaptic terminal and causes release of the Excitatory (o) or Inhibitory (•) transmitter.
2. Combination of the excitatory transmitter with the postsynaptic receptors produces a localized depolarization, the excitatory post synaptic potential (EPSP), through an increase in permeability of ALL (small) ions (Na+ and K+ chiefly involved). The inhibitory transmitter causes a selective increase in permeability to the smaller ions (K+ and Cl- chiefly involved) resulting in a localized hyperpolarization, the inhibitory post synaptic potential (IPSP).
3. The EPSP initiates a conducted NAP in the post synaptic neuron; this can however, be prevented by the hyperpolarization induced by a concurrent IPSP).

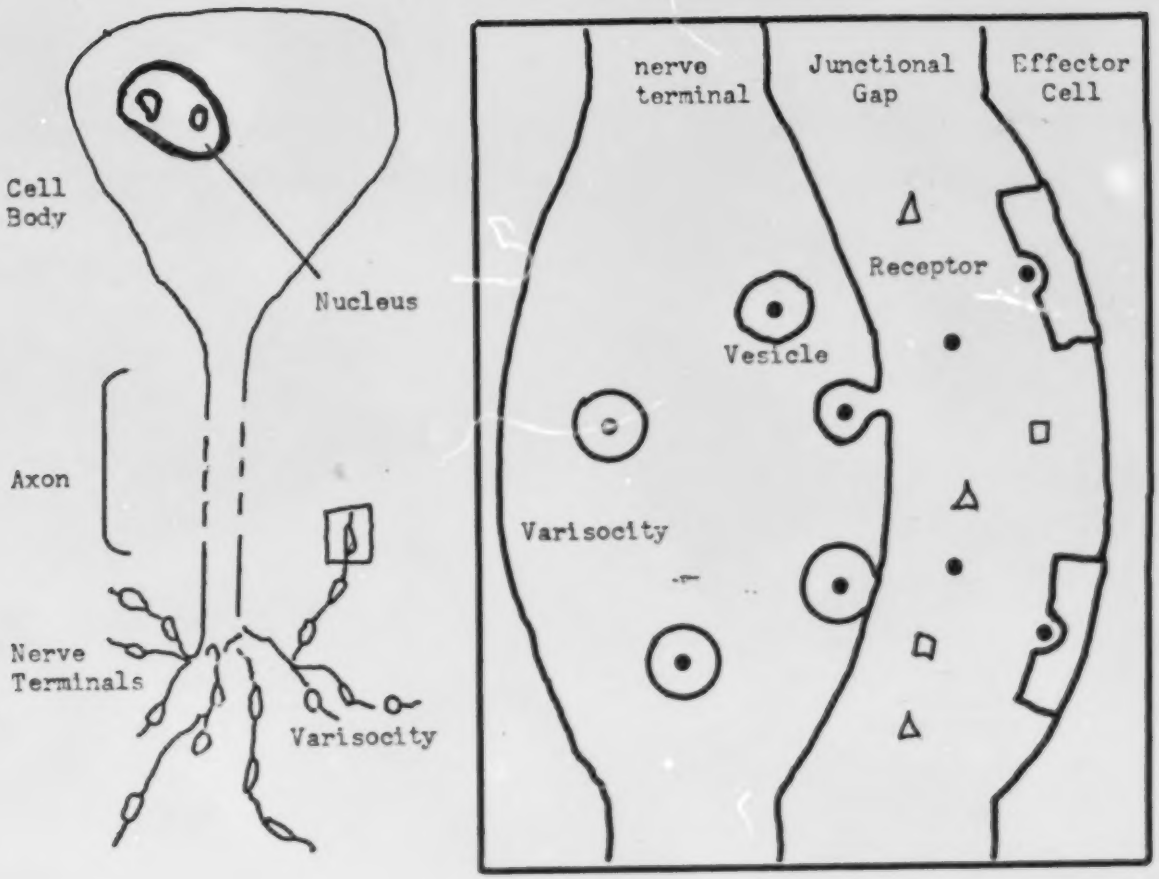
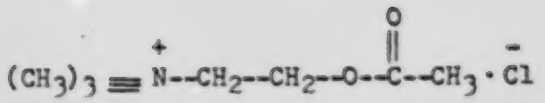
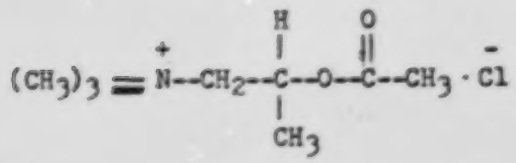


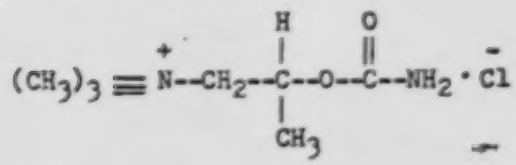
Fig. 9 Sympathetic Neuron, or nerve cell (a), consists of a cell body, a long axon and numerous nerve terminals studded with varicosities. Enzymes involved in the synthesis of the transmitters are made in the nucleus and transported down the axon to the varicosities, where the transmitters are manufactured and stored. A varicosity and its junction with another cell are enlarged (b). The transmitter (dots) is stored in vesicles. When the nerve is excited and depolarized, vesicles move to the cell membrane and fuse with it, releasing transmitters into the junctional gap. The transmitter reaches receptors on the effector cell that recognize only it, not any other chemicals (black shapes) that are present in the gap.



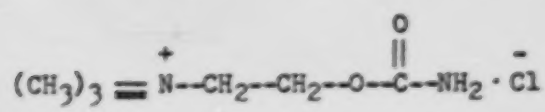
Acetylcholine chloride



Methacholine (Mecholyl) chloride



Bethanechol (Urecholine) chloride



Carbachol (Doryl) chloride

Fig.10 All drugs in this group are quarternary amines. Replacement of the acetyl group by carbamate protects the drug against cholinesterases and thus prolongs its half-life in the body. Substitution in the β carbon, as in acetyl-β-methyl choline, protects against the action of the nonspecific cholinesterase.

Bethanechol (Urecholine), methacholine (Metholyl), and furtrethonium iodide (Furmethide) have many of the actions of acetylcholine on smooth muscles and glands without affecting significantly ganglia and skeletal neuromuscular transmission.

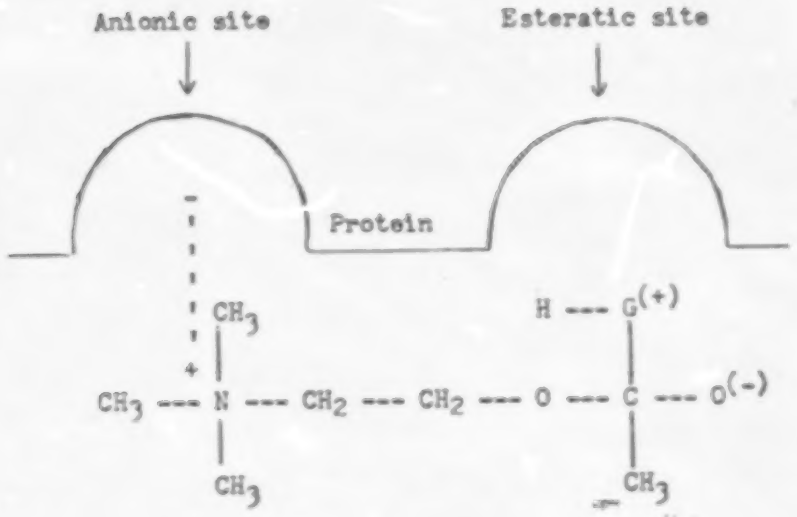


Fig. 11 Interaction of acetylcholine and acetylcholinesterase. (From Wilson, I. B.: Neurology supp.1 8:41, 1958.)

Responses of Effector Organs

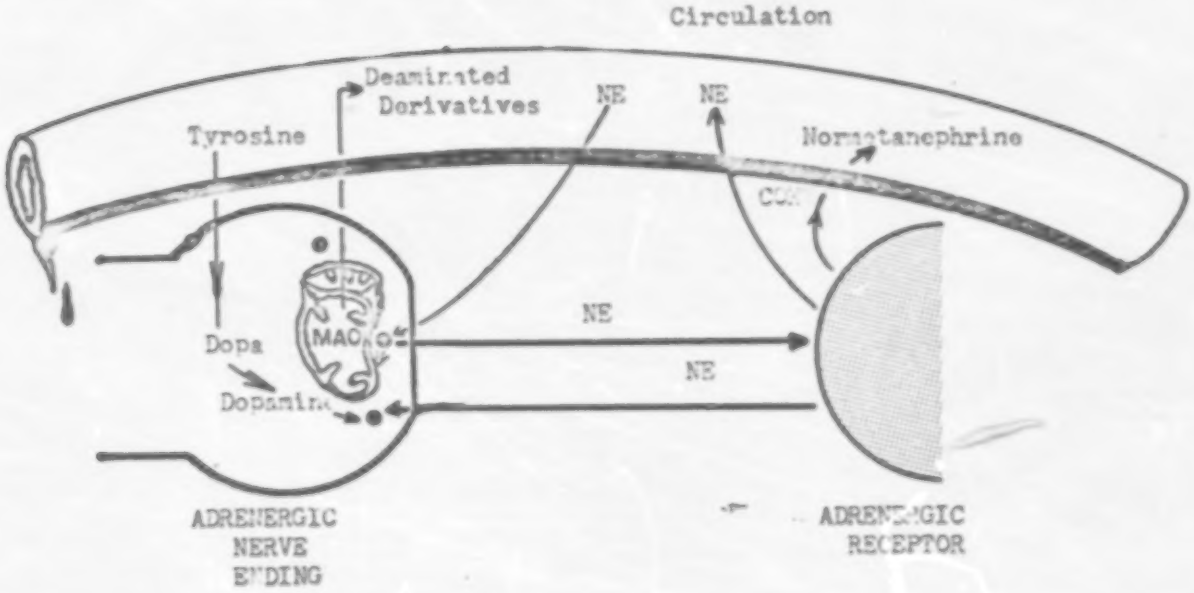


Fig. 12 Formation, uptake, and metabolism of norepinephrine at adrenergic nerve endings. Norepinephrine in the granulated vesicles is mainly released from the endings by action potentials in the sympathetic nerves. However, some of the norepinephrine constantly diffused from the granules to the mitochondria, where it is oxidized to deaminated derivatives. Norepinephrine in the vesicles is formed from dopamine, taken up from the circulation, and taken up again after it is released from the endings (re-uptake).

The granulated vesicles in the adrenergic nerve endings not only convert dopamine to norepinephrine; they also take up some preformed norepinephrine from the circulation. In addition, they take up large quantities of the norepinephrine released from the endings by action potentials. This re-uptake of released norepinephrine is a major mechanism by which norepinephrine is removed from the vicinity of autonomic endings. The hypersensitivity of the sympathetically denervated structures is probably explained in part on this basis; after the adrenergic neurons are cut, their endings degenerate. Consequently, there are no granules to take up norepinephrine, and more is available to stimulate the receptors of the autonomic effectors.

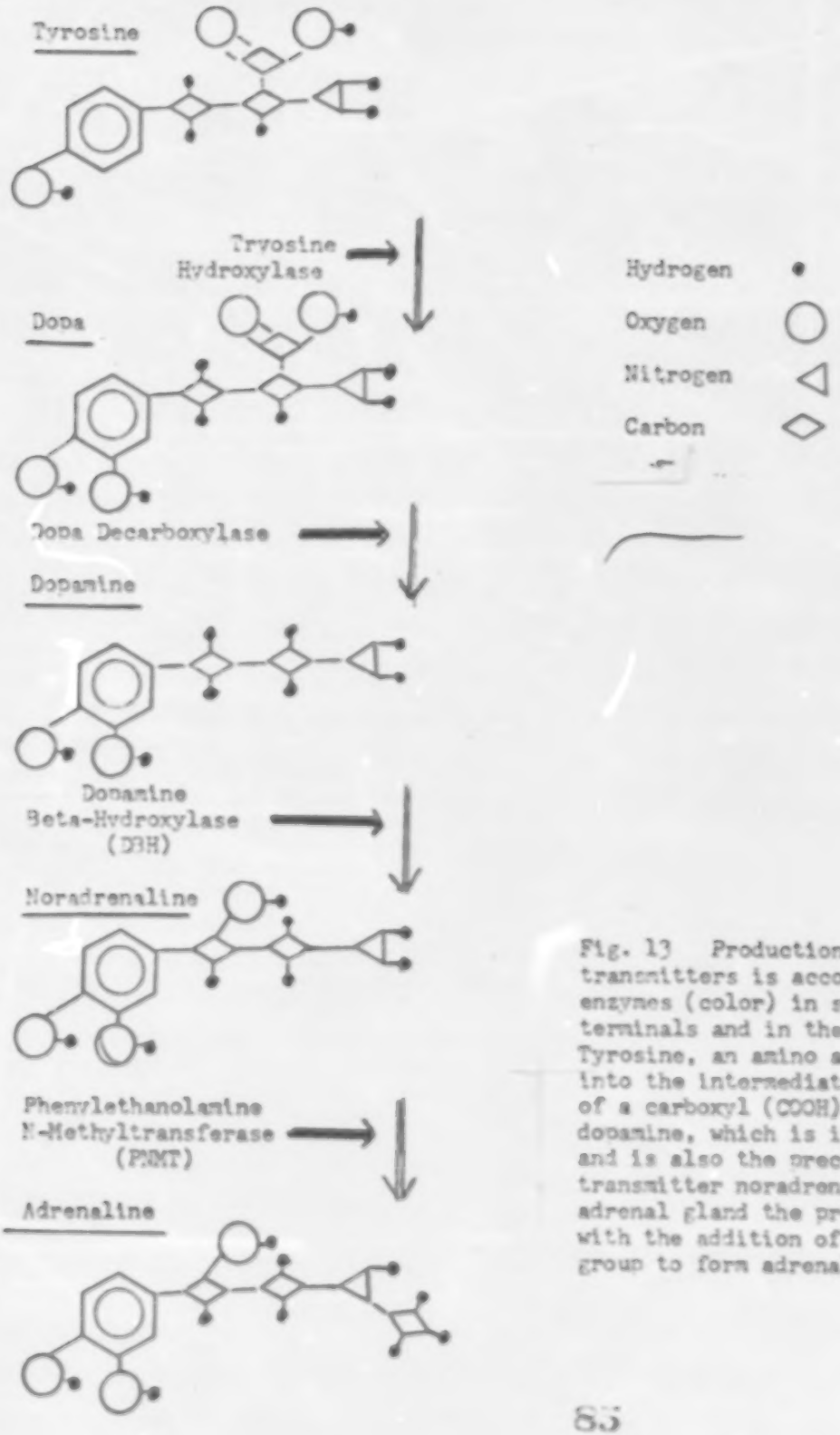
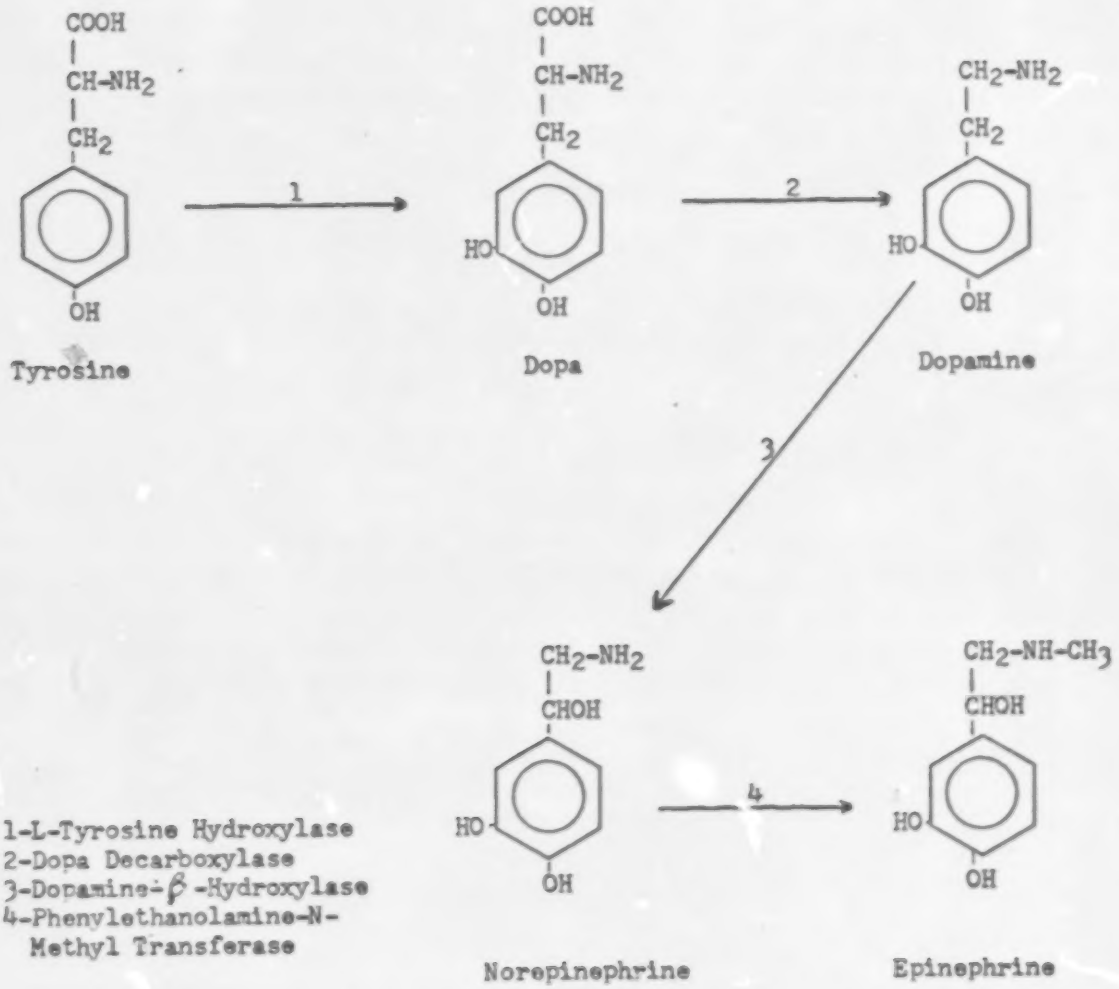


Fig. 13 Production of catecholamine transmitters is accomplished by four enzymes (color) in sympathetic-nerve terminals and in the adrenal gland. Tyrosine, an amino acid, is transformed into the intermediate dopa. Removal of a carboxyl (COOH) group forms dopamine, which is itself a transmitter and is also the precursor of the transmitter noradrenaline. In the adrenal gland the process continues with the addition of a methyl (CH_2) group to form adrenaline. (Ref. 4)

Synthesis of norepinephrine and epinephrine



1-L-Tyrosine Hydroxylase
2-Dopa Decarboxylase
3-Dopamine-β-Hydroxylase
4-Phenylethanolamine-N-Methyl Transferase

Fig. 13a

Synthesis of norepinephrine and epinephrine

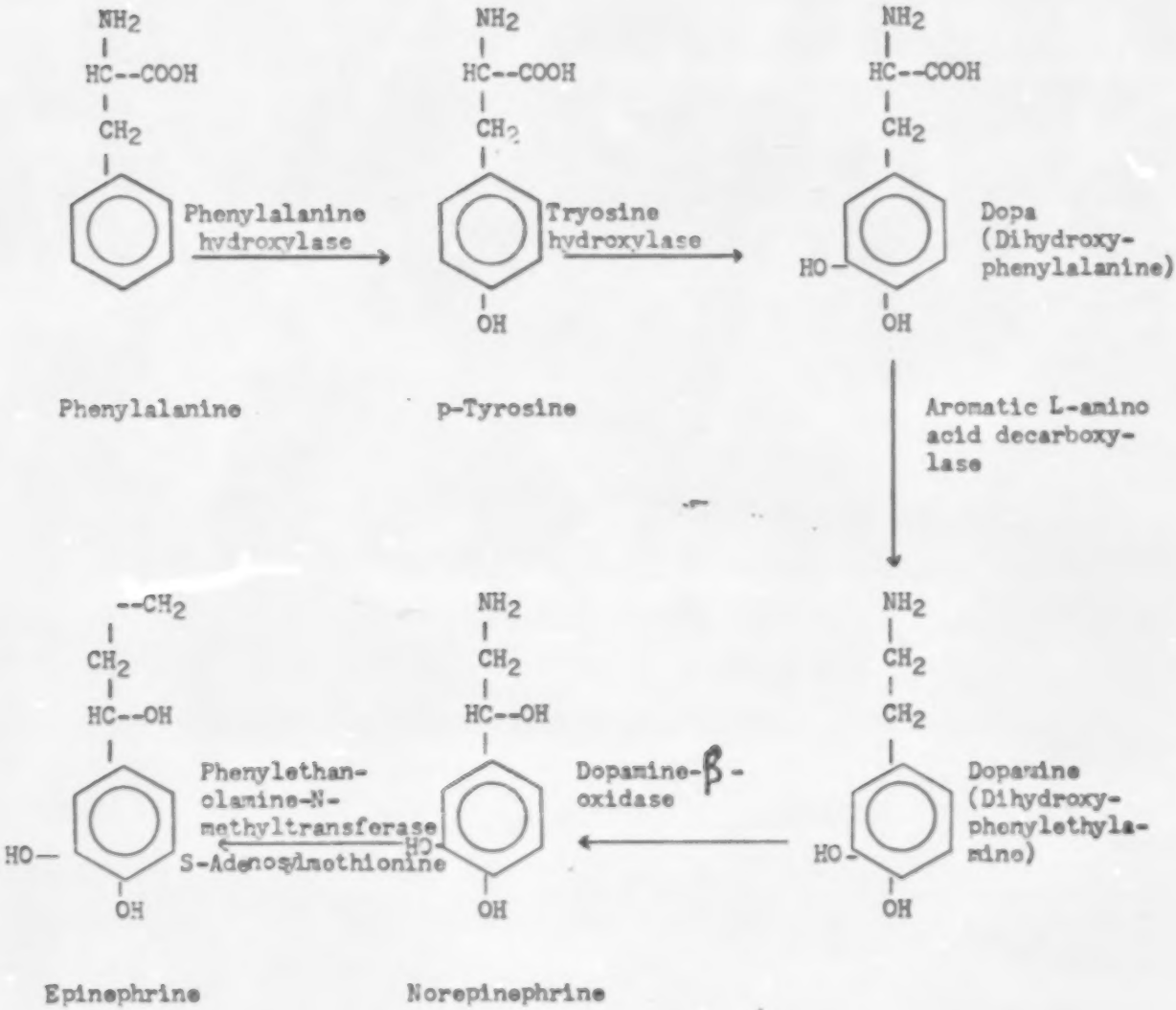


Fig. 14 Biosynthesis of catecholamines.

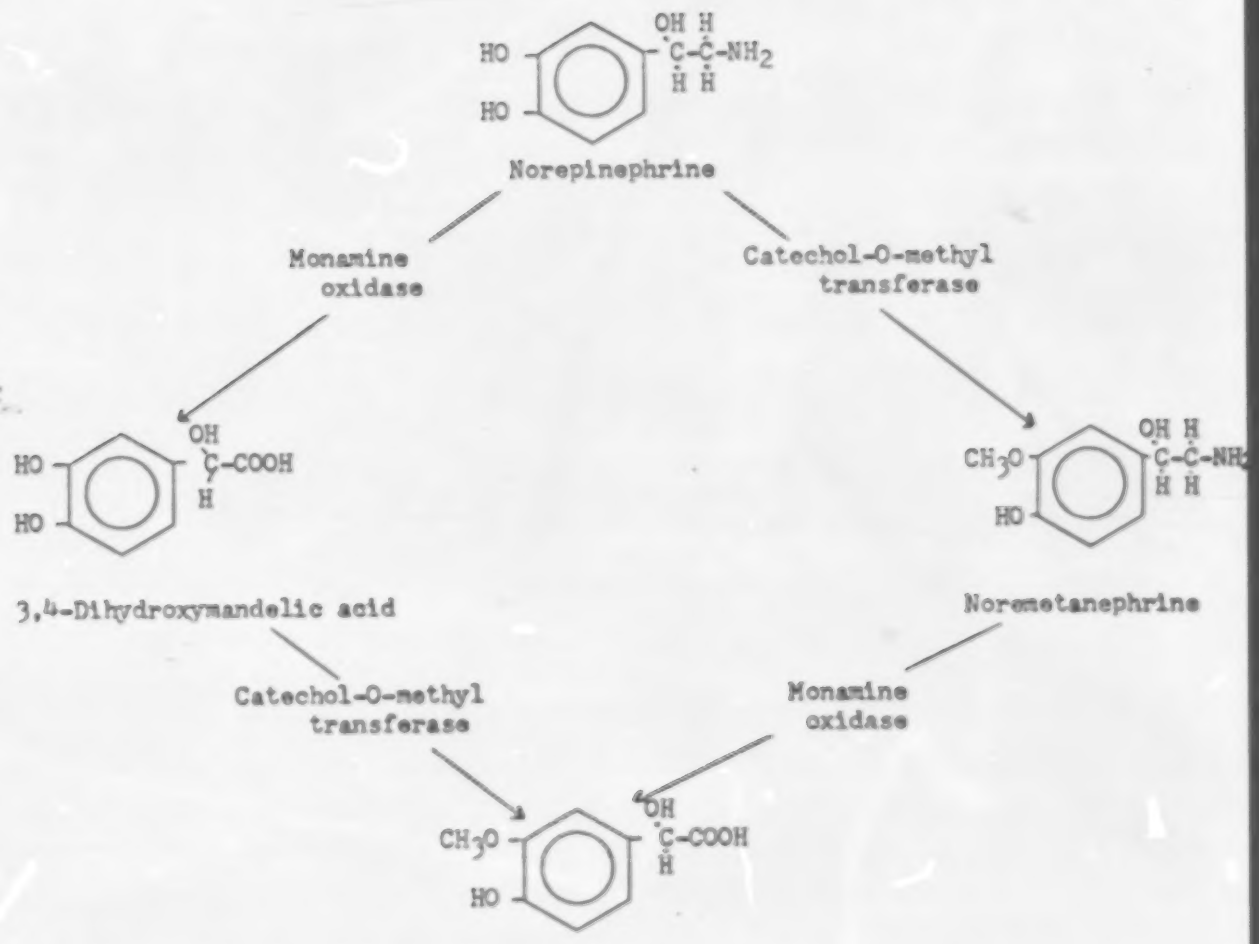


Fig. 15 Major pathways of norepinephrine metabolism. Monamine oxidase actually changes norepinephrine and normetanephrine to the corresponding mandelic aldehydes. These products are then transformed to the mandelic acids by aldehyde dehydrogenase.

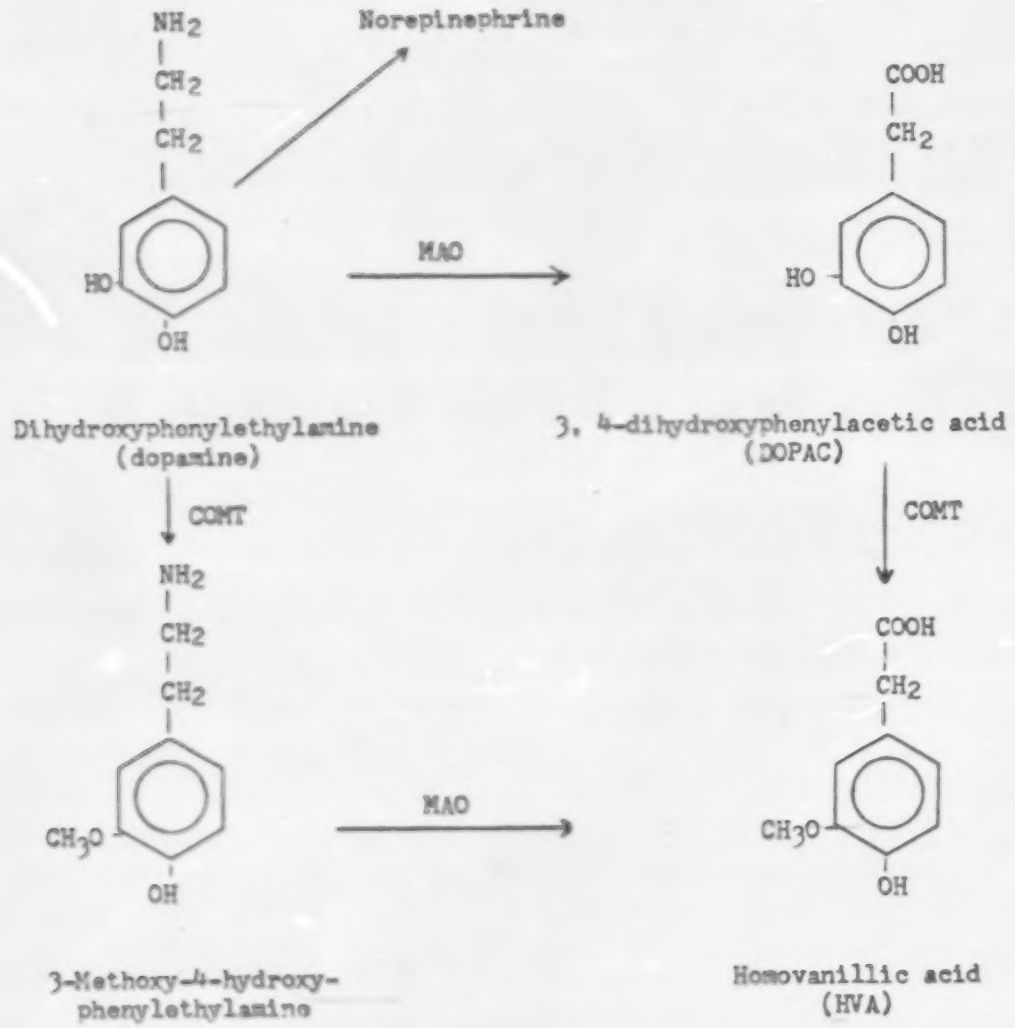


Fig. 16 Catabolism of dopamine. MAO, monoamine oxidase; COMT, catechol-o-methyltransferase.

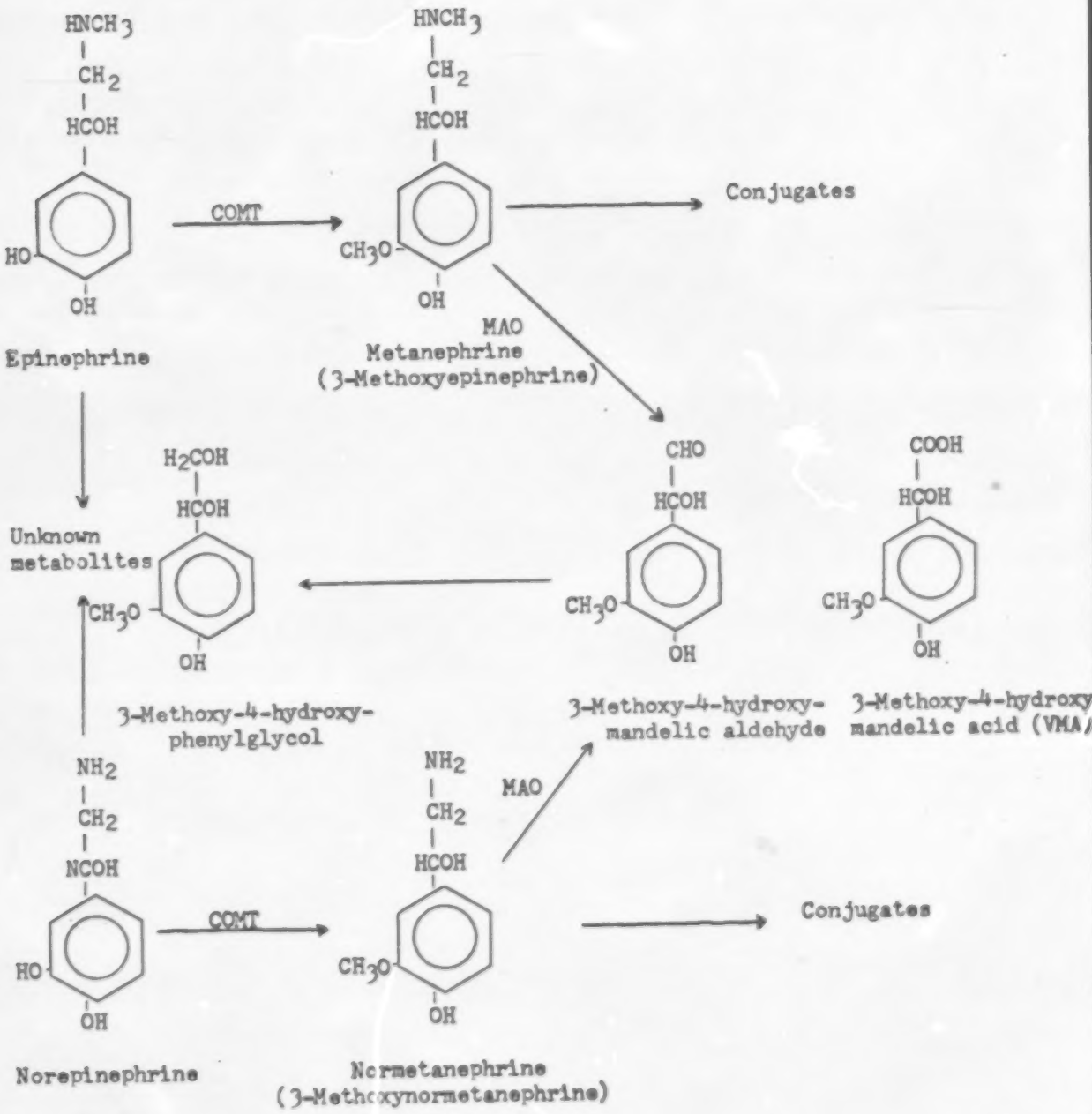


Fig. 17 Catabolism of circulating epinephrine and norepinephrine. The main site of catabolism is the liver. The conjugates are mostly glucuronides and sulfates.

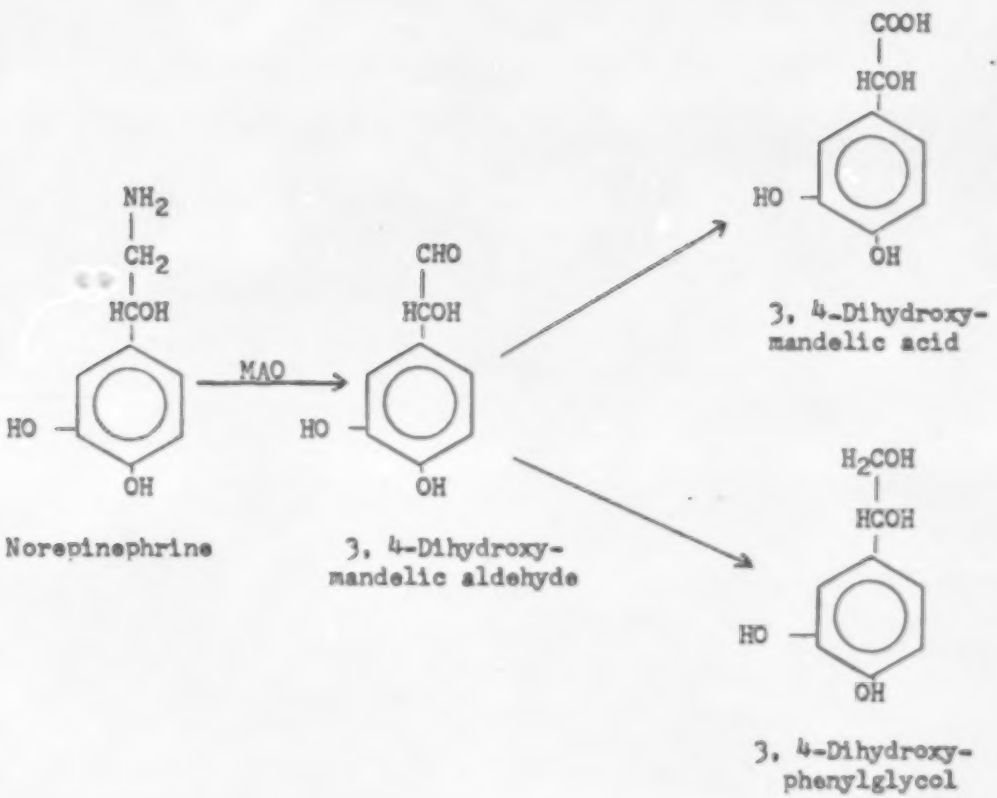


Fig. 18 Catabolism of norepinephrine in adrenergic nerve endings. The acid and the glycol enter the circulation and may be subsequently o-methylated to VMA and 3-methoxy-4-hydroxyphenylglycol. (MAO, monoamine oxidase; COMT, catechol-o-methyltransferase).

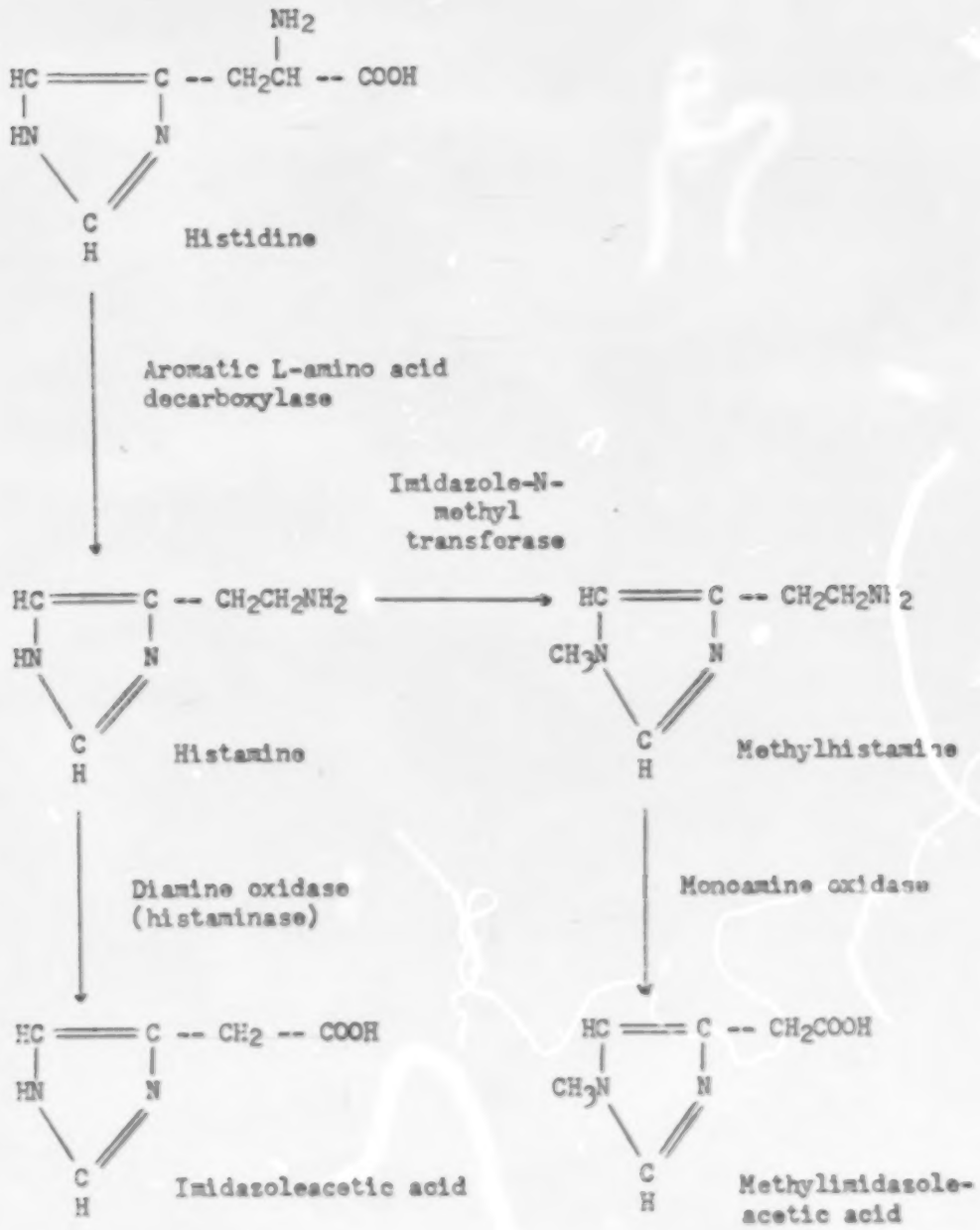
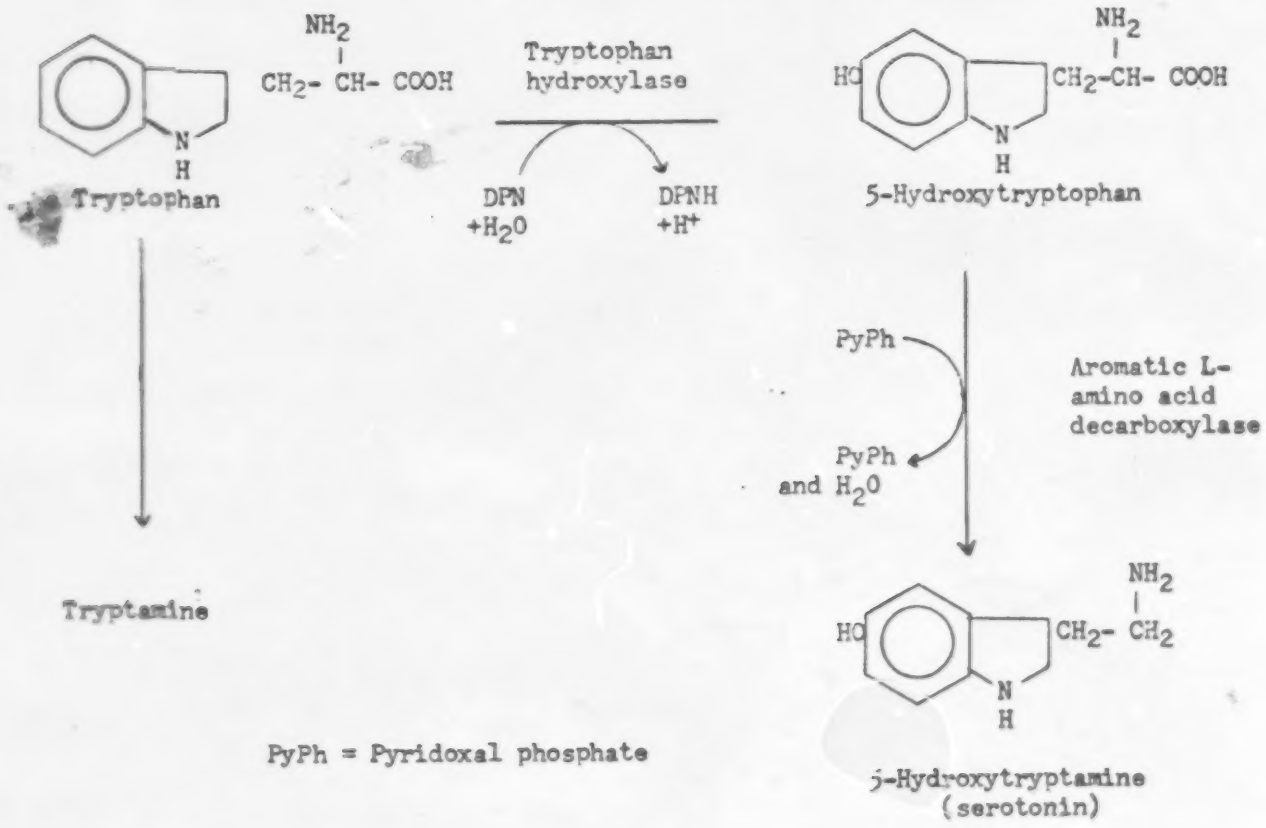


Fig. 19 Synthesis and catabolism of histamine.



PyPh = Pyridoxal phosphate

Fig. 20 Biosynthesis of serotonin. Note that the same enzyme catalyzes the decarboxylation of 5-hydroxytryptophan and DOPA (see Fig.14).

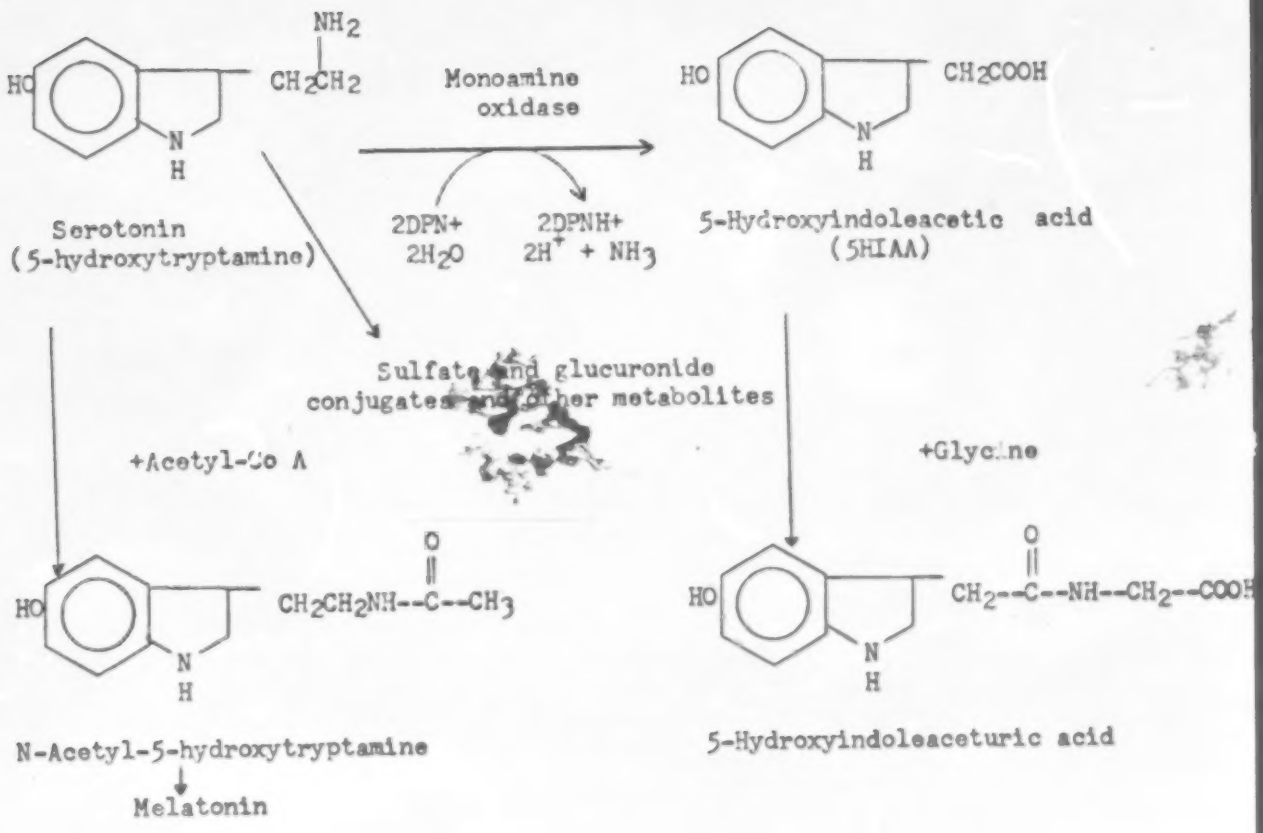


Fig. 21 Catabolism of serotonin. In the oxidative deamination catalyzed by monoamine oxidase, an aldehyde is formed first and then oxidized to the corresponding acid. Some of the aldehyde is also reduced to the corresponding alcohol. The heavy arrow indicates the major metabolic pathway.

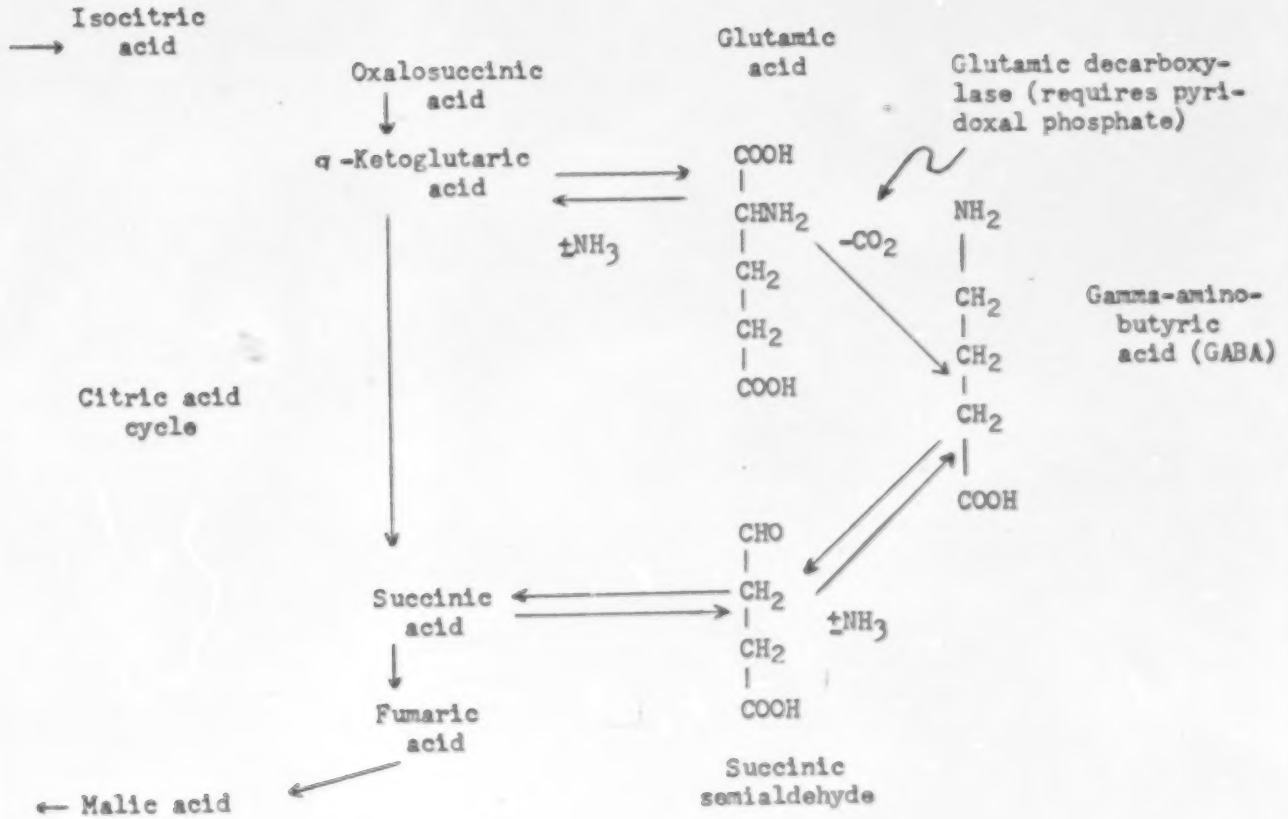


Fig. 22 Formation and metabolism of gamma-aminobutryric acid.

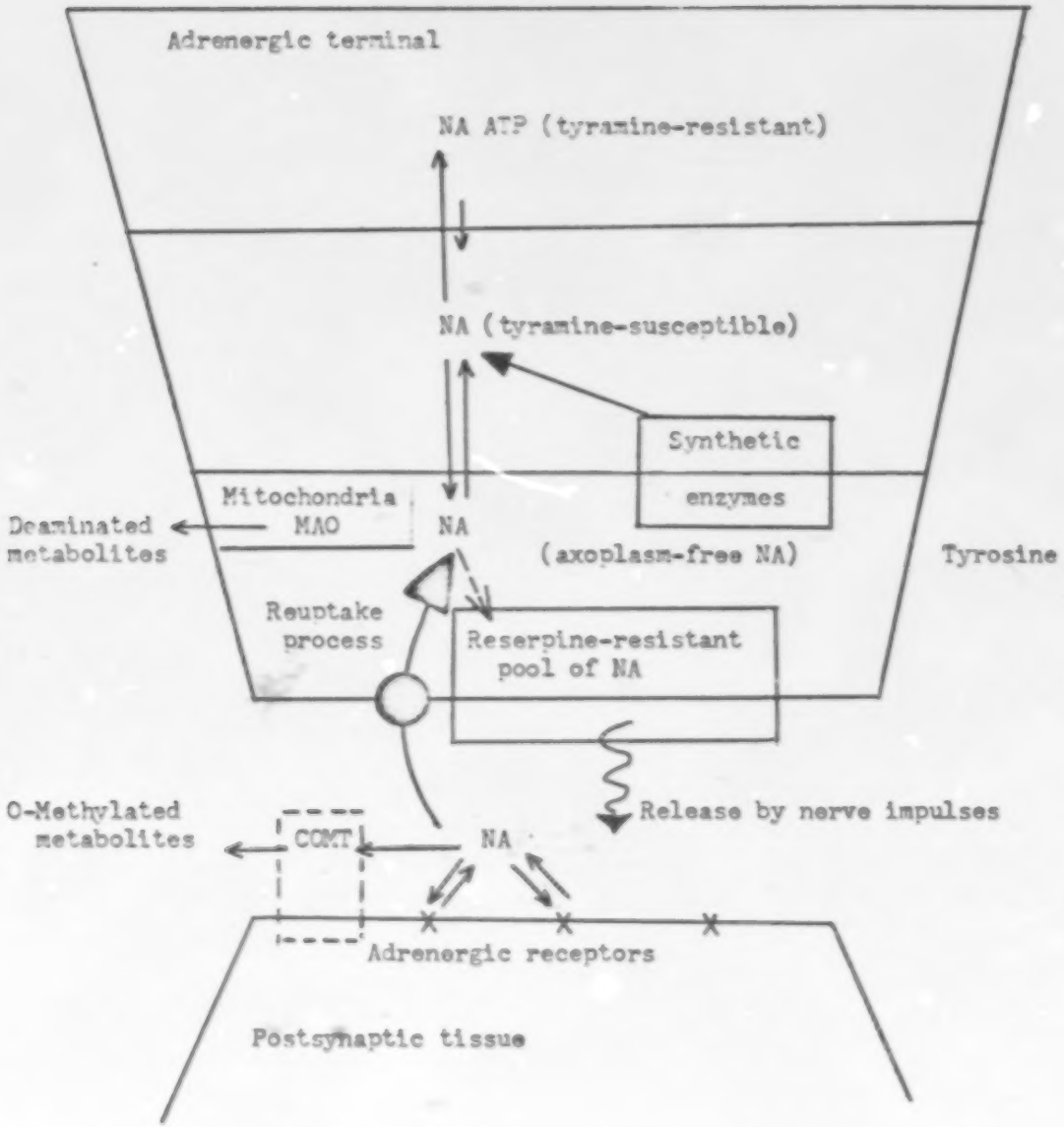


Fig. 23 A scheme indicating the inter-relationships of the stores of noradrenaline (NA) within an adrenergic nerve terminal. From Iversen 1967.

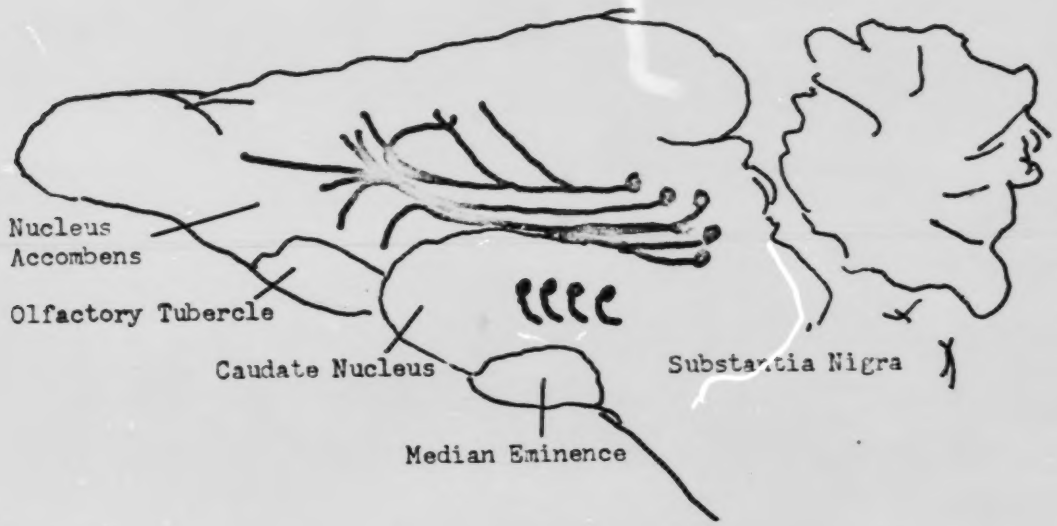


Fig. 24 Dopamine tracts, the main bundles of nerves containing dopamine, are shown (black) in a drawing of a longitudinal section along the midline of the rat brain. The cell bodies are concentrated in the substantia nigra, and the axons project primarily to the caudate nucleus. A dopamine deficiency in that region causes Parkinsonism, which can be treated with dopa.

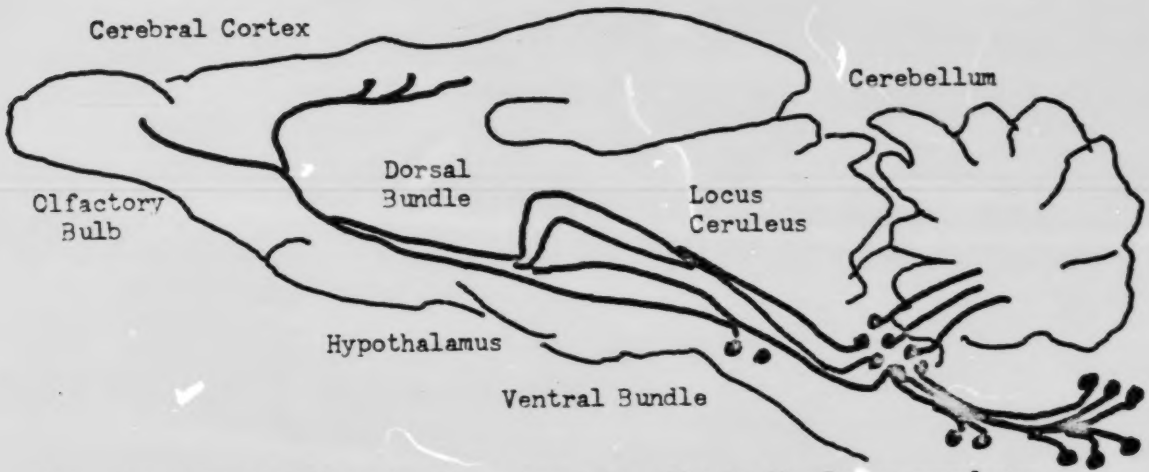


Fig. 24a Noradrenaline tracts arise primarily in the locus ceruleus and reach many brain centers, including the cerebellum, cerebral cortex and hypothalamus. Illustrations on this page are based on maps made by Urban Ungerstedt of Royal Caroline Institute in Sweden.

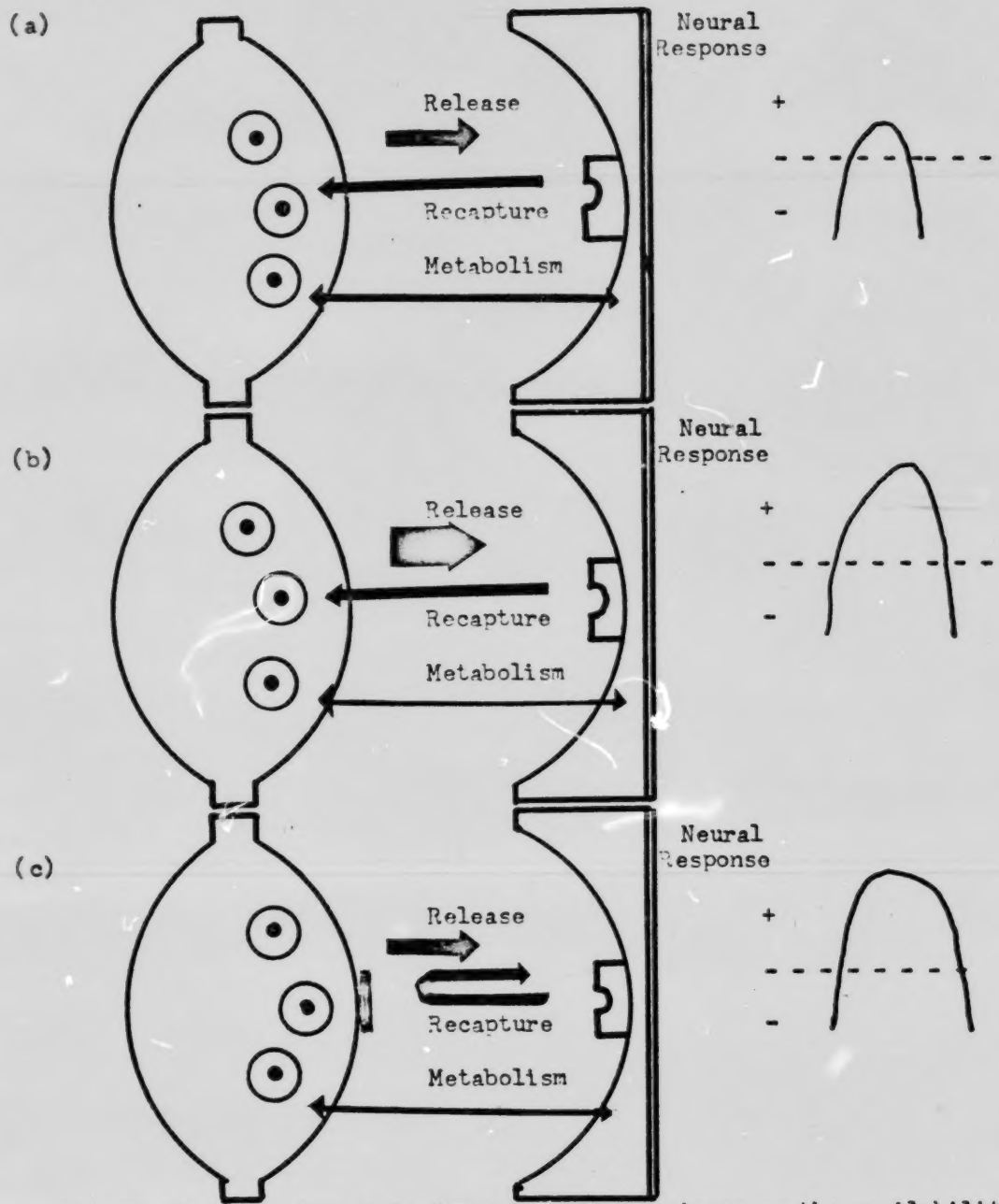


Fig.25 Certain adrenergic drugs increase or decrease the availability of noradrenaline at the adrenergic receptor. Normal release, recapture and metabolism (colored arrows) are illustrated, with a curve representing the normal response of a postjunctional cell (a). Antidepressant drugs enlarge that response in several ways, all of which increase the availability of noradrenaline at the synapse. Amphetamine does so by promoting the release of noradrenaline (b). Amphetamine and imipramine and related drugs block recapture (c).

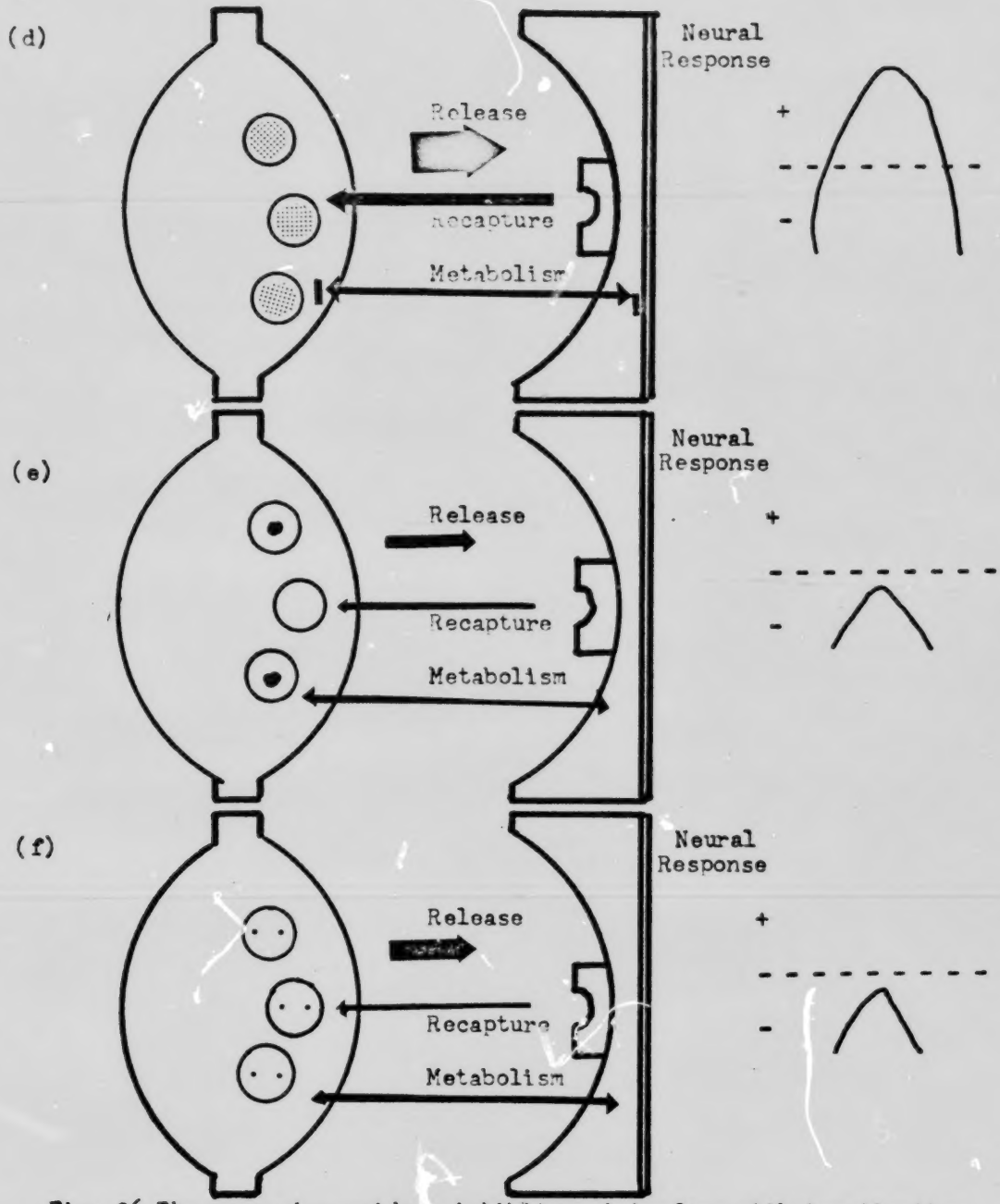


Fig. 26 The monoamine-oxidase inhibitors interfere with inactivation through metabolism (d). Conversely, reserpine, which reduces blood pressure and may induce depression, reduces the response by depleting the noradrenaline in storage (e); alphamethyldopa and other "false transmitters" are stored in the vesicles with noradrenaline and released with it, diluting its effect (f).

TABLE I

AMINE AND SUBSTANCE P CONTENT OF SELECTED PORTIONS OF THE HUMAN BRAIN. DATA COMPILED FROM VARIOUS AUTHORS

	Norepinephrine	Dopamine	5-Hydroxy-tryptamine	Histamine	Substance P (U/gm)
	(µg/gm fresh tissue)				
Amygdala	0.21	0.6	0.26	‡	‡
Caudate nucleus	0.09	3.5	0.33	0.5	85
Putamen	0.12	3.7	0.32	0.7	‡
Globus pallidus	0.15	0.5	0.23	0.6	‡
Thalamus	0.13	0.3	0.26	0.4	12
Hypothalamus	1.25	0.8	0.29	2.5	102
Substantia nigra	0.21	0.9	0.55	‡	699

‡ No data.

TABLE II

KNOWN AND SUSPECTED SYNAPTIC TRANSMITTER AGENTS AND "NEURAL HORMONES"

Substance	Locations Where Substance is Secreted	
	Known	Suspected
Acetylcholine	Myoneural junction Preganglionic autonomic endings Postganglionic parasympathetic endings Postganglionic sweat gland and muscle vasodilator endings	Motor cortex Thalamus Caudate nucleus Supraoptic, paraventricular nuclei Mamillary bodies Motor nuclei of vagus and hypoglossal nerves Cerebellar cortex Posterior gray substance of spinal cord Retina
Norepinephrine	Postganglionic sympathetic endings	Hypothalamus and environs
Dopamine	. .	Caudate nucleus, putamen, retina, hypothalamus
Serotonin	. .	Hypothalamus and environs
Substance P	. .	Hypothalamus, substantia nigra, retina
Histamine	. .	Hypothalamus
Vasopressin	Posterior pituitary	. .
Oxytocin	Posterior pituitary	. .
Anterior pituitary hormone releasing and inhibiting factors (CRF, TRF, LRF, GHRF, RSHRF, PIF)	. .	Median eminence of hypothalamus
Inhibitory mediator	. .	Spinal cord, cerebral cortex, etc.
Mediator for presynaptic inhibition	. .	Spinal cord
Prostaglandins	. .	Cerebral cortex, cerebellum, spinal cord

TABLE III

BRAIN CONTENT OF GABA AND A NUMBER OF PROBABLE TRANSMITTER AGENTS AT SYNAPSES IN THE CNS

	DOG					RAT
	Acetylcholine µg/gm*	Substance P units/gm*	Serotonin µg/gm*	Norepinephrine µg/gm*	Histamine µg/gm*	GABA† µg/gm
Cerebral cortex--somasthetic	2.8	‡	‡	0	0	210
Cerebral cortex--motor	4.5	19	0.02	0.18	. .	. .
Caudate nucleus	2.7	46	0.10	0.06	0	‡
Thalamus	3.0	13	0.02	0.16	0	‡
Hypothalamus	1.8	70	0.25	1.03	30	380
Hippocampus	‡	15	0.05	‡	‡	‡
Medulla	1.6	25	0.03	‡	‡	200
Cerebellum	0.2	2	0.01	0.07	0	160
Spinal cord	1.6	29	0	‡	0	‡
Sympathetic ganglia	30	7	0	6.00	5	‡
Area postrema	‡	460	0.24	1.04	‡	‡

* Data on dog from various authors, compiled by Paton: Ann. Rev. Physiol. 20: 431, 1958.

† Data on rat GABA (gamma-aminobutyric acid) from Berl & Waelsch: J. Neurochem. 3: 161, 1958.

‡ No data.

TABLE IV

Effect of iproniazid on concentration of serotonin in brains of normal and reserpine treated rabbits (Ref. 15)

Drug	Brain Serotonin (ug/gram, average)	Effect
None	0.55	-------
Reserpine	0.10	Sedation
Iproniazid	0.63	None
Iproniazid followed by Reserpine	0.42	Excitement
Reserpine followed by Iproniazid	0.10	Sedation

TABLE V

Drug	Dosage
Phenelzine (Nardil)	15-60 mg
Nealamide (Niamid)	50-200 mg
Isocarboxazid (Marplan)	30-60 mg

Appendix A

Glossary of Drugs

Generic Name	Brand	Company
	ANTIPSYCHOTIC AGENTS	
Phenothiazines		
Acepromazine	Notensil, Plegicil	Clin-Byla
Acetophenazine	Tindal	Schering
Butaperazine	Repoise	Robins
Carphenazine	Proketazine	Wyeth
Chlorpromazine	Thorazine	Smith, Kline & French
Dixyrazine	Esucos	Union Chimiques Beige
Fluphenazine	Prolixin, Permitil	Squibb, White
Mepazine	Pacatal	Warner
Mesoridazine	Serentil	Sandoz
Methophenazine	Frenelon	Medimpex
Methotrimeprazine	Veractil, Levoprome, Nirvan	May & Baker, Lederle United Drug
Methoxypromazine	Tentone	Lederle
Perphenazine	Trilafon	Schering
Pipamazine	Mornidine	Searle
Piperacetazine	Quide	Pitman-Moore
Prochlorperazine	Compazine	Smith, Kline & French
Promazine	Sparine	Wyeth
Promethazine	Phenergan	Wyeth
Propericiazine	Neuleptil	Rhone Poulenc
Propiomazine	Largon	Wyeth
Prothipendyl	Timovan	Ayerst
Thiazinamium	Multergan	Rhone Poulenc
Thiethylperazine	Torecan	Sandoz
Thiopropazate	Dartal	Searle
Thioproperazine	Majeptil	Rhone Poulenc
Thioridazine	Mellaril	Sandoz
Trifluoperazine	Stelazine	Smith, Kline & French
Triflupromazine	Vesprin	Squibb
Butyrophenones		
Dehydrobenzperidol	Innovar	McNeil
Haloperidol	Serenace, Haldol	Searle, McNeil
Thioxanthenes		
Chlorprothixene	Taractan, Solatran	Roche, Warner
Clopenthixol	Sordinol	Ayerst

Appendix A (con't)

Glossary of Drugs

Generic Name	Brand	Company
Thioxanthenes		
Thiothixene	Navane	Pfizer
Xanthiol	Daxid	Pfizer
Reserpines		
Deserpidine	Harmonyl	Abbott
Rescinnamine	Moderil	Pfizer
Reserpine	Serpasil and others	Ciba and others
MOOD-ACTIVE DRUGS		
Tricyclics		
Amitriptyline	Elavil	Merck
Desipramine	Pertofran, Norpramin	Geigy, Lakeside
Imipramine	Tofranil	Geigy
Nortriptyline	Aventyl	Lilly
Opipramol	Ensidon	Geigy
Protriptyline	Vivactil	Merck
Trimipramine	Surmontil	Rhone-Poulenc
MAO Inhibitors		
Etryptamine	Monase (withdrawn)	Upjohn
Ipromiazid	Marsilid (withdrawn)	Roche
Isocarboxazid	Marplan	Roche
Mebanazine	Actomol	Imperial Chemical Industry
Nialamide	Niamide	Pfizer
Pargyline	Eutonyl	Abbott
Phenelzine	Nardil	Warner
Pheniprazine	Catron (withdrawn)	Lakeside
Tranylcypromine	Parnate	Smith, Kline & French
Stimulants		
Amphetamine	Benzedrine	Smith, Kline & French
Dextro-Amphetamine	Dexedrine	Smith, Kline & French

Appendix A (con't)

Glossary of Drugs

Generic Name	Brand	Company
Stimulants		
Deanol	Deaner	Riker
Methamphetamine	Amphedroxyn, Desoxyn	Lilly, Abbott
Methylphenidate	Ritalin	Ciba
NONBARBITURATE MINOR TRANQUILIZERS AND SEDATIVES		
Acetylcarbromal	Sedamyl	Riker
Azacyclonol	Frenquel	Merrell
Benactyzine	Suavitil	Merck, Charp & Dohme
Benzquinamide	Quantril	Pfizer
Buclizine	Softran, Vibazine	Stuart, Pfizer
Captodiame	Suvren	Ayerst
Chlordiazepoxide	Librium	Roche
Chlormethazanone	Trancopal	Sterling-Winthrop
Diazepam	Valium	Roche
Ectylurea	Levanil	Upjohn
Emylcamate	Striatran	Merck
Hydroxyphenamate	Listica	Armour
Hydroxyzine	Vistaril, Atarax	Pfizer, Roerig
Mephenoxalone	Trepidone, Lenetran	Lederle, Lakeside
Meprobamate	Miltown, Equonil	Wallace, Wyeth
Oxanamide	Quiactin	Merrell
Oxazepam	Serax	Wyeth
Phenaglycodol	Ultran	Lilly
Tybamate	Solacen	Wallace
NONBARBITURATE HYPNOTICS		
Ethchlorvynol	Placidyl	Abbott
Ethinamate	Valmid	Lilly
Glutethimide	Donden	Ciba
Methaqualone	Quaalude	Roren
Methylpentynol	Dormison	Schering
Methyprylon	Noludar	Roche

APPENDIX B (Pages 95 - 124)

```
     Lesson name ---- uimc23
     Disk pack ------ minerva
     Starting date --  09/08/73
***  Last edited ----  07/17/74  12.00.13.
     by ----  obrien    1- 6  uicc 37
```

Press the corresponding number to change an entry.

SECURITY CODES:

a. To change lesson	--	**********
b. To inspect lesson	--	blank--OPEN TO ALL
c. To access common	--	**********
d. To -use- lesson	--	blank--OPEN TO ALL
e. To -jumpout-	--	**********

1. Author name -- mcdougall

2. Department -- uimc med center

3. Telephone number -- (312) 343 7200 x2676

4. Discipline -- na

5. Grade level -- na

6. One line description of lesson --

functions and operations of neurotransmitters

xmitchars) 16

```
 0 sp
 1 a    (
 2 b    |
 3 c    )
 4 d    \
10 j    <
11 k    >(&:)
12 l    >
13 m    &:
19 s    >
24 x    ~^(
26 z    ~
27 0    .
28 1    .
29 2    °
64 sp
```

```
    BLOCK D = title                    SPACE = 280
 1  unit     title
 2  at       48,424
 3  size     3
 4  write    Neurotransmitters
 5  at       200,344
 6  write    and
 7  at       176,248
 8  write    Their
 9  at       136,152
10  write    Operation
11  at       2539
12  size     0
13  write    by W. D. McDougall
14
15
16           Programmed by:
17                    Michael T. O'Brien
18  at       328
19  write    Part I
```

BLOCK C = transmit1

```
1   unit    goals
2   calc    v4$-1  $$ flag for ⊛
3   calc    v3$-1  $$ flag for test
4   charset uimc23,xmitchars
5   *jump    cast1
6   at      808
7   write         The purpose of this lesson is to give you a
8               working knowledge of the way in which the synaptic
9               junctions at the ends of nerve axons perform their
10              functions.
11
12              We will first introduce the major concepts of
13              the junction process, and then show you a model of
14              how the process operates.  Then you will be given
15              a test based on your comprehension of the process.
16  do      next
17  unit    intro
18  next    basics1
19  at      508
20  write         The work on just what goes on at a synapse
21              began quite early, but developed rather slowly due
22              to the extremely complex nature of the (microscopic)
23              process.  It was first discovered in 1901* that
24              injection of adrenal gland extract into tissues con-
25              taining nerves belonging to the sympathetic nervous
26              system stimulated these tissues.  From this early
27              base has been built up all of our knowledge of the
28              workings of nerve synapses, the nature and function
29              of neurotransmitters, and the nature and function
30              of all the related enzymes and activating substances
31              involved in nerve cell communication.
```

BLOCK: c = transmit1

```
 1  at        2510
 2  write     *
 3  at        2511
 4  write     For a list of references on the subject matter,
 5            press the -TERM1- key, which is a shifted key, and
 6            type "refer" (no quotes) at the "what term? >"
 7            which appears.  You may do this at (almost) any
 8            point in the lesson.
 9  do        next
10  unit      refer
11  term      refer
12  at        205
13  write     Axelrod, Julius,  "Neurotransmitters", Scientific A
              merican
14            June, 1974
15  do        next
16  end
17  unit      basics1
18  window    3201,1064
19  at        105
20  write           This is a model of what the end of a nerve loo
              s
21            like.  The bulge is called a "varicosity", and the
22            co.lection of such bulges at the end of a nerve cel
23            looks a great deal like a root system.
24                 The corresponding body on the right side is th
25            so-called "effector cell"; it is the cell which the
              nerve
26            ending is to stimulate.  We will build on this pic
              ure
27            as we go on.
```

BLOCK C = transmit

```
1   do      transmit
2   at      1923
3   write   varicosity
4           (end of nerve
5           cell)
6   at      1655
7   write   effector
8           cell
9   do      next
```

BLOCK d = transmit2

```
 1  unit     tbas1
 2  back     v3,basics1,basics4
 3  do       transmit
 4  at       705
 5  writec   v3↕Now for a quick one to make sure you're awake.↕↕
 6  at       1806
 7  write    What is this?
 8  do       back
 9  arrow    1823
10  ans
11  write    varicosity
12  answer   varicosity
13  or
14  answer   nerve <end,of,cell,varicose>
15  write    Fine!
16  wrong    effector <cell>
17  write    That's the
18           other one.
19  wrong    synapse
20  write    Ok, but what is
21           this part of it?
22  arrow    1147
23  at       845
24  write    ...and what is
25           this?
26  mode     rewrite
27  ans
28  write    effector cell
29  specs
30  mode     write
31  answer   effector <cell>
```

BLOCK d = transmit2

```
 1  write    Just right!
 2  do       next
 3  wrong    nerve <cell>
 4  write    Could be, but
 5           what is the
 6           general term?
 7  wrong    varicosity
 8  write    Hardly! That's
 9           that ← thing
10           over there!
11  unit     basics2
12  window   3201,1064
13  do       transmit
14  do       trans1
15  draw     193,160;202,160;202,150;202,160;2818
16  at       2913
17  write    vacuole
18  at       405
19  write         The vacuoles in the nerve cell tip contain the
20       substances which are important in the stimulation
21       process.   The most important of these are the
22       neurotransmitters, which are the substances which
23       (eventually) stimulate or inhibit the effector cell.
24  window
25  draw     705;722
26  do       next
27  unit     basics3
28  do       transmit
29  do       trans1
30  do       trans2
31  at       105
```

```
 1  write       The effector cell, on its part, has so-called
 2              "receptor sites", which are locations the cell whic
 3              can detect, and are activated by, the neurotransmit
                ers.
 4  draw        1148;1248;1250;1248;855
 5  at          749
 6  write       receptor
 7                  site
 8  do          next
 9  unit        tbas2
10  back        basics2
11  do          transmit
12  do          trans1
13  do          trans2
14  at          320
15  write       Now, let's make sure
16              you got that:
17  mode        rewrite
18  at          1617
19  write       What is this? →
20  mode        write
21  do          back
22  arrow       1723
23  ans
24  write       vacuole
25  answer      vacuole
26  write       Right!
27  wrong       receptor <site>
28  write       That's the
29              other one.
```

BLOCK d = transmit2 SPACE - 41

```
 1  arrow    646
 2  mode     rewrite
 3  at       1233
 4  write    ...and what
 5           is this? →
 6  mode     write
 7  ans
 8  write    "receptor site"
 9  answer   receptor <site>
10  write    Fine!
11  wrong    vacuole
12  write    That's the
13           object in
14           the varicosity.
```

BLOCK e = transmit3

```
 1  unit     basics4
 2  at       105
 3  write         Now we will show you how the actual transmissio
            n
 4            of a nerve impulse takes place:
 5  window   3201,1064
 6  pause    5,keys=next
 7  erase
 8  do       trans
 9  at       1701
10  write    Note that the receptor
11           site took only one
12           of the three chem-
13           icals which came out
14           of the vacuole.
15           The receptor site
16           is very specific;
17           it will only accept
18           a particular kind
19           of neurotransmitter.
20  pause    8,keys=next
21  at       1142
22  erase    10,7
23  at       842
24  write    The process whereby the
25            contents of the
26  at       1044
27  write    vacuole leave the
28            nerve cell is
29  at       1246
30  write    called
```

BLOCK e = transmit3 SCROLL - 95

```
 1  at      1246
 2  write   called
 3           "exocytosis".
 4  draw    323,143;327,132;339,132;327,132;1347
 5  do      next
 6  at      3115
 7  mode    rewrite
 8  write   Press -BACK- to see the simulation again.
 9  back    basics4
10  mode    write
11  unit    differ
12  do      final
13  at      105
14  write        Note that one of receptor sites showed activity
                ,
15              while the other did not.  This is because there are
16              different sorts of receptors, sensitive to differen
17              sorts of neurotransmitters.  We might call the two
18              types represented here A-receptors and D-receptors.
19  mode    write
20  do      label
21  do      next
22  next    v3,test1,test2
23  unit    label
24  size    2
25  at      1447
26  write   A
27  at      2749
28  write   D
29  size    0
30  unit    test1
```

BLOCK e = transmit3 SPACE = 95

```
 1  unit    test1
 2  back    basics4
 3  calc    v3≠0  $$flag for -back-s.
 4  at      1212
 5  write        Now we are going to test you on what you
 6           have just seen.  You may press the -BACK- key
 7           at any time to review the simulation, but if
 8           you do, you will have to take the test over
 9           again from the beginning.  You may press -BACK-
10           now to review, if you wish.
11  do      back
12  do      next
13  unit    test2
14  do      tbas1
```

BLOCK 1 = transmit+ ORDER - 79

```
 1  unit     test3
 2  window   3201;864
 3  do       transmit
 4  do       trans1
 5  do       trans2
 6  window
 7  do       back
 8  back     basics4
 9  draw     1532;305
10  at       303
11  write    This is a(r)
12  draw     319;335
13  arrow    317
14  ans
15  mode     erase
16  draw     1532;305
17  mode     write
18  at       505
19  write    vacuole
20  answer   vacuole
21  mode     erase
22  draw     1532;305
23  mode     write
24  at       505
25  write    Fine!
26  wrong    varicosity
27  at       335
28  write    What part of the
29           varicosity is it?
30  arrow    717
31  draw     1245;703
```

```
      BLOCK f = transmit4                    scroll  2
 1    at       305
 2    write         In order to transport the neurotransmitter sub
 3              stances to the receptor site, the vacuole will firs
 4    draw     505;525
 5    arrow    503
 6    eraseu   helperas
 7    ans
 8    do       t4ans
 9    specs    roorder
10    do       helper
11    goto     ntries≥3,t4ans,x
12    answer   (go,travel,migrate,head,move)<to,toward,towards,the
               cell> (wall,membrane,surface,boundary,border)
13    write    Fine!
14    do       trans3
15    wrong    burst
16    write    No, it has to be at the
17             cell wall before it can
18             burst.
19    wrong    (migrate,move)
20    write    ...to where?
21    unit     t4ans
22    at       603
23    write    "move to the cell wall"
24    unit     helper
25    at       703
26    writec   order↕↕There's a word out of order.↕
27    at       803
28    writec   spell↕↕There's a word misspelled.↕
29    at       903
30    writec   extra↕↕There's something extra here.↕
```

BLOCK f = transmit4 SPACE = 79

```
 1   writec   extra##There's something extra here.#
 2   at       1003
 3   writec   entire##There's something missing here.#
 4   unit     helperas
 5   mode     erase
 6   do       t4ans
 7   do       helper
 8   mode     write
 9   at       805
10   erase    23,3
```

BLOCK g = transmit5

```
 1  unit     test5
 2  at       303
 3  erase    60,4
 4  at       805
 5  erase    5
 6  at       305
 7  write         Next, the vacuole          and the neurotransm
    tters
 8             move to the receptor site proper.
 9  arrow    328
10  ans
11  at       530
12  write    "bursts"
13  specs    nookno
14  answer   (bursts,breaks,busts,opens)
15  at       630
16  write    Great!
17  do       trans4
18  do       next
19  unit     test5.5
20  window   3201;964
21  do       final
22  at       305
23  write    The process by which the vacuole breaks is called:
24  arrow    520
25  ans
26  write    "exocytosis"
27  specs
28  writec   ntries≥3$and$judged≥0:"exocytosis" is the answer.::
29  answer   exocytosis
30  write    Just right!
```

BLOCK g = transmit5 SPACE = 167

```
 1  answer   exocytosis
 2  write    Just right!
 3  do       next
 4  no
 5  write    Try again.
 6  unit     test6
 7  next     cast1
 8  window   320;1064
 9  do       final
10  mode     write
11  do       back
12  back     basics4
13  at       305
14  write         Of the chemicals that leave the vacuole, the
15           receptor site will accept
16  draw     435;450
17  arrow    433
18  ans
19  write    only one
20  specs    bumpshift
21  answer   <just,only> one
22  wrong    (two)
23  at       725
24  write    That's how many receptors we've
25           discussed, but how many
26           neurotransmitters will a
27           single receptor accept?
28  wrong    (three,four,five)
29  write    That's way too many.
30  no
31  write    How many?
```

```
1  unit    cast1
2  at      1005
3  write        It is now time to introduce the cast of charact
           ers
4           in our little drama.  So far we have been referring
           to
5           neurotransmitters in a generic sense.  Now we will
6           identify them more particularly.
7  at      2010
8  write   At present only two substances are recognized
9           without doubt as being neurotransmitters:
10
11
12                              ACETYLCHOLINE
13
14                                  and
15
16                              NORADRENALINE
17 do      next
18 unit    cast2
19 at      710
20 write        The reason for the scarcity of recognized
21          neurotransmitters lies in the strict criteria
22          which a true neurotransmitter must fulfill.
23          These are:
24
25               1) Nerves must have the necessary enzymes to
26          produce the chemical.
27               2) Nerves must liberate the chemical when
28          stimulated.
29               3) The chemical should react with specific
```

BLOCK h = cast1 SPACE - 60

```
1                    2) Nerves must liberate the chemical when
2           stimulated.
3                    3) The chemical should react with specific
4           receptor sites on the effector (or post-junctional)
5           cell.
6                    4) Mechanisms should be present which rapidly
7           terminate the action of the chemical (so that a
8           nerve may be fired several times in rapid succession
9           without providing just a single, broad response).
10  at      2810
11  write   Only acetylcholine and noradrenaline have so far
12          been found to satisfy all these criteria.
13  do      next
14  unit    cast3
15  inhibit erase
16  at      710
17  write   These are not the only entries in the race, however.
18          It is expected that other chemicals will be found
19          which satisfy the criteria for neurotransmitters.
20          Some other sustpects are listed below, in the
21          right-hand column.
22  at      1512
23  write   KNOWN
24
25          acetylcholine
26          noradrenaline
27  at      1537
28  write   "PUTATIVE"
29
30          dopamine
31          adrenaline
```

```
      BLOCK h = cast1                                    STACK    00
 1              dopamine
 2              adrenaline
 3              serotonin
 4              octopamine
 5              histamine
 6              gamma aminobutyric acid
 7              glutamic acid
 8              aspartic acid
 9              glycine
10  at          2810
11  write       Don't bother to memorize the entries in the right-
12              hand column.  Only the first three are widely used
13              in experimentation.
14  do          next
```

BLOCK 1 = cast2 SPACE - 70

```
 1  unit     cast4
 2  at       112
 3  write    Nerves which contain noradrenalin are called
 4           "noradrenergic" nerves; those which contain
 5           acetylcholine are called "cholinergic" nerves.
 6  unit     tcast1
 7  next     tcast2
 8  inhibit  erase
 9  at       1012
10  write    Name the two substances which are known to be
11           neurotransmitters;
12  arrow    1315
13  ans
14  write    acetylcholine and noradrenaline
15  specs    noorder
16  answer   acetylcholine <and> noradrenaline
17  write    Fine!
18  answer   acetylcholine
19  calc     v5=-1
20  jump     other
21  answer   noradrenaline
22  calc     v5=0
23  jump     other
24  no
25  nextnow  spell,cast1,x
26  unit     other
27  next     tcast2
28  at       1335
29  write    and
30  arrow    1340
31  join     v5,norad.acet
```

BLOCK 1 = cast2 SPACE 46

```
 1  arrow    1340
 2  join     v5,norad,acet
 3  no
 4  nextnow  spell,cast1,x
 5  unit     norad
 6  answer   noradrenaline
 7  unit     acet
 8  answer   acetylcholine
 9  unit     tcast2
10  erase
11  at       1012
12  write    Nerves which contain noradrenaline are called
13                                  nerves.
14  arrow    1110
15  ans
16  write    noradrenergic
17  specs
18  writec   ntries≥3$and$judged≥0♦"noradrenergic" is the term.♦♦
19  answer   noradrenergic
20  wrong    adrenergic
21  at       1212
22  write    Close, but you forgot the "nor-" prefix.
23  arrow    1610
24  at       15.2
25  write    Nerves which contain acetylcholine are called
26                                  nerves.
27  ans
28  write    cholinergic
29  specs
30  writec   ntries≥3$and$judged≥0♦"cholinergic" is the term.♦♦
31  answer   cholinergic
```

```
      BLOCK 1 = cast2                          SPACE =  48
 1  writec  ntries=3$and$judged=0:"cholinergic" is the term.::
 2  answer  cholinergic
 3  write   Fine!
 4  wrong   acetylcholinergic
 5  write   Actually, "cholinergic" is the term.
 6  unit    finish
 7  at      1215
 8  write   You have finished the lesson at this point.
 9                          Hope you enjoyed it!
10  end     lesson
11  unit    trans
12  at      101
13  write       Here is a model of a varicosity at the end of
14          nerve axon:
15  do      transmit
16  catchup
17  pause   3,keys=next
18  at      401
19  write       Here are the vacuoles which contain the neuro-
20          transmitters:
21  do      trans1
22  catchup
23  pause   3,keys=next
24  at      701
25  write       Here are the receptor sites:
26  do      trans2
27  pause   5,keys=next
28  at      1001
29  write       Now one of the
30          vacuoles migrates to
31          the edge of the
```

BLOCK 1 = cast2

```
1  write        Now one of the
2             vacuoles migrates to
3             the edge of the
4             cell wall;
5  do         trans3
6  pause      5,keys=next
7  at         1501
8  write           and bursts.
9  do         trans4
```

BLOCK 1 = pictures

```
 1  unit     transmit
 2  draw     428;1028
 3  circle   92,124,358,356,311
 4  circle   212,364,176,148,212
 5  draw     434;1034
 6  circle   92,356,358,184,229
 7  circle   165,171,180,41,-45
 8  circle   158,420,-22,147,172
 9  circle   92,124,-6,49,4
10  draw     445;1045
11  circle   126,472,392,198,235
12  circle   238,186,184,26,-30
13  circle   104,480,8,148,184
14  unit     trans1
15  circle   10,264,264
16  do       junk
17  circle   10,216,176
18  do       junk
19  circle   10,224,96
20  do       junk
21  at       215,130
22  writec   v4$ (88) $$
23  unit     trans2
24  draw     1146;1244;1548;1451;skip;2453;392,135;368,79
25           393,67
26  unit     trans3
27  mode     rewrite
28  doto     1move,v1÷215,308
29  at       v1,130
```

BLOCK j = pictures SPACE - 112

```
 1  doto     1move,v1÷215,308
 2  at       v1,130
 3  write    ⊛
 4  1move
 5  unit     trans4
 6  mode     erase
 7  at       308,130
 8  write    ⊛
 9  mode     write
10  circle   8,324,138,32,291
11  at       320,130
12  write    ⁂
13  mode     erase
14  at       320,130
15  write    ⁂
16  mode     rewrite
17  doto     2move,v1÷1,40
18  at       320+7v1/6,130-7v1/6
19  write    .
20  at       320+8v1/6,130-5v1/6
21  write    .
22  at       320+9v1/6,130-v1/2
23  write    ∘
24  2move
25  at       380,110
26  write    ∘
27  at       373,95
28  write    .
29  circle   10,384,114,73,-114
30  draw     379,104;367,80
31  unit     junk
```

BLOCK j = pictures

```
 1  unit     junk
 2  calc     v1←wherex
 3           v2←wherey
 4  at       v1-15,v2+5
 5  write    ..
 6  at       v1-18,v2
 7  write    ...
 8  at       v1-13,v2-5
 9  write    ..
10  unit     final
11  calc     v4←0  $$ flag for ⊛
12  do       transmit
13  do       trans1
14  do       trans2
15  window
16  mode     erase
17  draw     387,122;379,104
18  mode     rewrite
19  at       380,110
20  write    .
21  circle   10,384,114,73,-114
22  unit     next
23  calc     v1←mode
24  mode     rewrite
25  at       3225
26  write    Press -NEXT-.
27  mode     v1,erase,rewrite,write
28  unit     back
29  calc     v1←mode
30  mode     rewrite
31  at       3118
```

BLOCK 3 - pictures

1	at	3118
2	write	Press -BACK- to review.
3	mode	v1,erase,rewrite,write

```
     Lesson name ---- uimc33
     Disk pack ------ alice
     Starting date --  06/28/74
***  Last edited ----  07/10/74  10.24.50.
     by ----  obrien    1- 4  uicc 37
```

Press the corresponding number to change an entry.

SECURITY CODES:

a. To change lesson	--	**********
b. To inspect lesson	--	blank--OPEN TO ALL
c. To access common	--	blank--OPEN TO ALL
d. To -use- lesson	--	blank--OPEN TO ALL
e. To -jumpout-	--	blank--OPEN TO ALL

1. Author name -- W. D. McDougall

2. Department -- v.a. hospital

3. Telephone number -- 343-7200 x2676

4. Discipline -- psychopharmacology

5. Grade level -- med school

6. One line description of lesson --

blocking effects of drugs on neurotransmitters

LESSON -- uimc23 HELP available

	BLOCK	NAME
	a.	address
	b	title
	c	transmit1
	d	transmit2
	e	transmit3
	f	transmit4
	g	transmit5
	h	cast1
	i	cast2
	j	pictures
chars	k	xmitchars
chars	l	xmitchars

LESSON -- uimc33 HELP available

BLOCK	NAME
a	address
b	block1
c	test1
d	block2
e	block3
f	drillunits
g	service
h	storage

```
      BLOCK a = address                    space - 150
1     ********************************************************************
2     ********************************************************************
3     ********************************************************************
4     ***
5     ***      please send this printout via
6     ***      intercampus courier service
7     ***                      to
8     ***      mike obrien
9     ***      221 ses
10    ***      chicago circle campus
11    ***
12    ***
13    ********************************************************************
14    ********************************************************************
15    ********************************************************************
16    unit     title
17    at       48,424
18    size     3
19    write    Neurotransmitters
20    at       200,344
21    write    and
22    at       176,248
23    write    Their
24    at       136,152
25    write    Operation
26    at       2539
27    size     0
28    write    by W. D. McDougall
29
30
31             Programmed by:
```

```
      BLOCK a = address                                  = 156
1                Programmed by:
2                        Michael T. O'Brien
3     at         328
4     write      Part II
```

```
      BLOCK b = block1                    SPACE -  72
 1  define   test=v3 ; $$flag for test
 2           drillno=v6
 3           pass=v7
 4           index$v8
 5           storbad(xx)=v(8+xx)
 6  calc     v2$-1 $$flag for -back-
 7           test$-1
 8  vocabs   mao,<drugs,drug,that,the,action,of,a,an,any,some>
 9           (inhibit,inhibits),(mao,mono*amine*oxidase)
10           (inhibitor,inhibitors)
11  unit     block
12  charset  uimc23,xmitchars
13  jump     block4
14  next     v2,block2,test1
15  window   3201;964
16  do       final
17  do       rel
18  do       rec
19  do       met
20  do       words
21  at       305
22  write    In this second lesson, we must consider the mechanis
             ms
23           by which a neurotransmitter does its work.  The diag
             ram
24           below shows the three major processes which affect t
             he
25           flow of neurotransmitters.
26  at       1001
27  write    release:
28  draw     where-8:where
```

```
1   at      1001
2   write   release:
3   draw    where-8;where
4   write     First, the neuro-
5           transmitter is released
6           by the nerve cell into
7           the junction gap.
8
9           resorption:
10  draw    where-11;where
11  write     Most of the
12          neurotransmitter
13          is reabsorbed by the
14          nerve cell; this effec-
15          tively deactivates it,to
16          prepare the synapse for
17          another firing.
18
19          metabolism:
20  draw    where-11;where
21  write     Some of the
22          neurotransmitter is
23          permanently destroyed
24          (metabolised) by the
25          nerve cell itself, or
26          by the effector cell.
27  do      next
28  unit    block2
29  at      703
30  write       We will need to remember these major processes
31          concerning neurotransmitters, since the actions
```

BLOCK b = block1

```
1   at      708
2   write       We will need to remember these major processes
3           concerning neurotransmitters, since the actions
4           of most drugs affecting the synapses produce
5           produce their effects by affecting one of these
6           three processes.
7
8               Note that we have not included absorption by
9           the receptor site among the three processes
10          affecting neurotransmitters.  In spite of the
11          fact that this is the most important event, it
12          uses such a small amount of neurotransmitter
13          that it is relatively unimportant in determining
14          the actual amount of neurotransmitter available
15          in the junction gap.
16  do      next
17  do      back
18  back    block
```

BLOCK 1 - test1

```
 1  unit     test1
 2  do       back
 3  back     block
 4  calc     v2≠0
 5  at       508
 6  write    '     Now for a test:
 7           You type in the name of the process at the
 8           appropriate » mark.
 9  window   2801;864
10  do       final
11  do       rel
12  do       rec
13  do       met
14  arrow    296,130
15  ans
16  at       24,130
17  write    "release"
18  specs
19  at       3045
20  writec   ntries≥3$and$judged≥0↕Try "release".↕↕
21  answer   release
22  at       450,130
23  write    Good!
24  no
25  at       3140
26  write    Try again...
27  arrow    272,97
28  ans
29  at       2603
30  write    "resorption"
31  specs
```

BLOCK 3 - TEST

```
1   specs
2   at        3045
3   writec    ntries≥3$and$judged≥0↕Try "resorption".↕↕
4   bump      -
5   answer    (resorption,reabsorption,recapture)
6   at        2654
7   write     Excellent!
8   wrong     metabolism
9   at        3120
10  write     That happens on both sides of the junction.
11  no
12  at        3140
13  write     That's not it.
14  arrow     2938
15  ans
16  at        2903
17  write     "metabolism"
18  specs
19  at        3045
20  writec    ntries≥3$and$judged≥0↕Try "metabolism".↕↕
21  answer    metabolism
22  at        2954
23  write     Great!
24  no
25  at        3140
26  write     No, try again
27  unit      block3
28  at        1012
29  write           Note that metabolism is one of the most
30              important of the processes involved in the
31              deactivation of neurotransmitters.
```

```
 1  write       Note that metabolism is one of the most
 2              important of the processes involved in the
 3              deactivation of neurotransmitters.
 4              If the metabolism of the neurotransmitters is
 5              blocked, they will remain active for a longer
 6              period of time, thereby effectively being
 7              amplified in their effect.
 8
 9              One of the enzymes chiefly responsible
10              for metabolising the neurotransmitters is
11              monoamine oxydase (MAO).
12  draw        2012;2029
13  at          2212
14  write       This enzyme is one of the most commonly
15              discussed in the literature, since many drugs
16              have their effect through inhibition of the
17              action of this enzyme.
18
19              This enzyme, in turn, is responsible for the
20              deactivation of a wide variety of compounds,
21              including noradrenaline, serotonin, dopamine,
22              and adrenaline.
```

BLOCK 4 BLOCK2

```
 1  unit     block4
 2  window   3201;964
 3  do       final
 4  do       rel
 5  do       rec
 6  do       met
 7  do       words
 8  at       305
 9  write         We will now examine the effects of some typical
10               examples of drugs on the neurotransmission process.
11  do       next
12  pause    keys=next
13  at       305
14  erase    59,2
15  at       305
16  write         If we examine the response of a normal
17               synapse to stimulation, we would see a peak
18               like the one below.
19  origin   30,240
20  bounds   100,100
21  frame
22  graph    22,110,response
23  scalex   3
24  scaley   1
25  delta    .2
26  do       norresp
27  end
28  unit     amphet
29  window   3201;864
30  do       final
31  do       bigrel
```

```
 1  do        final
 2  do        bigrel
 3  do        rec
 4  do        met
 5  do        test,wamphet,x
 6  frame
 7  scalex    2
 8  scaley    .55
 9  do        norresp
10  do        next
11  end
12  unit      imip
13  window    3201;864
14  do        final
15  do        rel
16  do        stoprec
17  do        met
18  at        288,85
19  write     |
              |
20  do        test,wimip,x
21  frame
22  do        norresp
23  end
24  unit      mono
25  window    3201;864
26  do        final
27  mode      write
28  at        268,262
29  do        junk
```

```
 1  at        268,262
 2  do        junk
 3  at        224,172
 4  do        junk
 5  at        230,92
 6  do        junk
 7  mode      rewrite
 8  do        bigrel
 9  do        rec
10  do        met
11  at        256,56
12  write     ▌
13  at        412,56
14  write     ▌
15  do        test,wmono,x
16  frame
17  do        norresp
18  end
19  unit      reserp
20  next      test,alpha,x
21  window    3201;864
22  do        final
23  mode      erase
24  at        225,175
25  do        junk
26  mode      rewrite
27  do        smalrel
28  do        smalrec
29  do        met
30  do        test,wreserp,x
```

```
 1  frame
 2  scalex  8
 3  scaley  3
 4  do      norresp
 5  end
 6  unit    wamphet
 7  at      305
 8  write   When amphetamine
 9  draw    where-11;where
10  write    is administered, the release of
11          noradrenaline is greatly increased.
12  unit    wimip
13  at      305
14  write   Imipramine
15  draw    305;315
16  write    and amphetamine both prevent the reab-
17          sorption of neurotransmitter by the nerve cell.
18  unit    wmono
19  at      305
20  write   The drugs which inhibit the metabolism of neurotran
            -
21          mitters by monoamine oxidase lead to increased stor
            ge
22          of neurotransmitters in the nerve cell, and a conse
23          quently larger release of them.
24  unit    wreserp
25  at      305
26  write   Reserpine
27  draw    305;314
28  write   , by reducing the amount of noradrenaline in
            storage, reduces the amount that is released by the
```

write , by reducing the amount of noradrenaline in storage, reduces the amount that is released by the nerve cell.

```
 1  unit     alpha
 2  window   3201;864
 3  do       final
 4  do       smalrec
 5  do       met
 6  do       test,walpha,x
 7  draw     312,153;360,153;360,147;368,155;360,163;360,158;312
              158
 8  do       smalrel
 9  draw     344,184;2144;2145;skip;2144;1652
10  at       1652
11  write    noradrenaline
12  draw     372,146;372,138;380,138;skip;372,138;1953
13  at       1853
14  write    false
15           transmitter
16  frame
17  scalex   4
18  do       norresp
19  unit     test2exp
20  calc     test=0
21  at       1010
22  write         You will now have a test on the various
23           means by which drugs interact with the activity
24           of neurotransmitters (in our case, noradrenaline).
25
26                You will be shown displays like those you have
27           just seen, but without the explanations at the top
28           of the screen.  You must provide the name of the
29           drug (or class of drugs) which produces the speci-
```

```
 1            drug (or class of drugs) which produces the speci-
 2            fied effect.
 3   do       next
 4   unit     test2
 5   calc     pass=-1
 6   setperm  5
 7   jump     test2drv
 8   unit     test2drv
 9   randp    drillno
10   jump     drillno,x,x,testamph,testimip,testmao,testres,testa
              ph $$ give test
11   modperm   $$list exhausted
12   jump     pass,x,testfin $$ finish if this was second round
13   calc     pass=0 $$set flag to second round
14   goto     test2drv $$ repeat test minus items correct on firs
               round
15   unit     testfin
16   do       empty,index=1,5 $$ get list of items wrong 2 times
17   jump     storbad(1),x,done,x $$ leave if all test items corr
              ct
18   calc     test=-1 $$set flag so he'll see writing
19   do       flasher,index=1,5 $$show teaching units again
20   calc     test=0 $$take away writing for test
21   jump     test2 $$take test again
22   unit     flasher
23   do       storbad(index),x,out,amphet,imip,mono,reserp,alpha
24   do       next
25   pause    keys=next
26   erase
27   unit     empty
28   randp    storbad(index)
```

BLOCK E - WALKS

```
 1  unit     empty
 2  randp    storbad(index)
 3  unit     out
 4  exit      $$leave if done with flashbacks
 5  unit     done
 6  at       1608
 7  write    Congratulations!  You answered all the items correc
              ly.
 8
 9           This is the end of the lesson.
10  end      lesson
11  unit     walpha
12  at       305
13  write         α-methyldopa
14  draw     310;322
15  write     and other "false transmitters" are chem-
16           ically similar to noradrenaline, and are stored wit
              it
17           in the nerve cell, thus diluting it when the nerve
              ires.
18           Less actual noradrenaline is released.
```

```
 1  unit     testamph
 2  do       amphet
 3  do       ques
 4  arrow    530
 5  specs    okspell,bumpshift
 6  nextnow  test2drv
 7  answer   (amphetamine,speed,uppers)
 8  write    Correct!
 9  remove   1
10  no
11  write    That's not right.
12  unit     testimip
13  do       imip
14  do       ques
15  arrow    530
16  specs    okspell,bumpshift
17  nextnow  test2drv
18  answer   (imipramine,amphetamine,speed,uppers)
19  write    Correct!
20  remove   2
21  no
22  write    That's not correct.
23  unit     testmao
24  do       mono
25  do       ques
26  arrow    530
27  specs    okspell,bumpshift
28  nextnow  test2drv
29  putd     ,-, ,
30  concept  inhibit mao
```

```
 1  putd     ,-, ,
 2  concept  inhibit mao
 3           mao inhibitors
 4  write    Correct!
 5  remove   3
 6  no
 7  write    That's not right.
 8  unit     testres
 9  do       reserp
10  do       ques
11  arrow    530
12  specs    okspell,bumpshift
13  nextnow  test2drv
14  answer   reserpine
15  write    Correct!
16  remove   4
17  no
18  write    That's not it.
19  unit     testalph
20  do       alpha
21  do       ques
22  arrow    530
23  specs    okspell,bumpshift
24  nextnow  test2drv
25  putd     ,-, ,
26  answer   false (transmitter,transmitters)
27  or
28  answer   (α,alpha) methyldopa
29  or
30  answer   (α,alpha) methyl dopa
```

```
 1  answer  (α,alpha) methyl dopa
 2  or
 3  answer  alphamethyldopa
 4  or
 5  answer  alphamethyl dopa
 6  write   Correct!
 7  remove  5
 8  no
 9  write   That's not correct.
10  unit    ques
11  mode    write
12  at      310
13  write   The drug(s) responsible for this situation is(are)
```

```
      BLOCK g = service
 1    use      uimc23,pictures
 2    unit     words
 3    at       312,130
 4    write    release
 5    draw     2340;2346
 6    at       288,98
 7    write    resorption
 8    at       2938
 9    write    metabolism
10    unit     norresp
11    funct    exp(-v1^2)sin(v1)+.007v1,v1≤0,3
12    unit     rel
13    draw     2340;2346;360,152;376,136;360,120;2446;2440
14    unit     smalrel
15    draw     2440;2446;360,122;368,130;360,138;360,133;312,133
16    unit     bigrel
17    draw     2440;2446;360,120;384,140;360,160;360,152;312,152
18    unit     rec
19    draw     2537;2636;2737;2636;2646
20    unit     smalrec
21    draw     2644;2639;312,104;skip;304,96;312,88
22    unit     met
23    draw     400,76;408,64;400,52;skip;280,76;272,64;280,52;skip;
               2835;2852
24    unit     stoprec
25    draw     2746;2741;skip;320,92;360,92;360,88;368,96
26             360,104;360,101;320,101;skip;320,71;360,71
27             360,80
28    circle   6,318,86,288,72
29    circle   15,318,86,82,278
      unit     help
```

BLOCK 8 = service

```
1  circle  6,318,86,288,72
2  circle  15,318,86,82,278
3  unit    help
4  calc    v5*mode
5  at      3120
6  write   Press -HELP- for help.
7  mode    v5,erase,rewrite,write
```

APPENDIX D (Pages 149 - 174)

Lesson name ---- uimc36
Dial pack ------ carmen
Starting date -- 07/25/74
*** Last edited ---- 07/26/74 13.16.08..
by ---- obrien 1- 5 uicc 37

SECURITY CODES:

a. To change lesson -- **********
b. To inspect lesson -- blank--OPEN TO ALL
c. To access common -- blank--OPEN TO ALL
d. To -use- lesson -- blank--OPEN TO ALL
e. To -jumpout- -- blank--OPEN TO ALL

1. Author name -- w.d. mcdougall

2. Department -- V. A. Hospital

3. Telephone number -- (312) 343-7200 x2676

4. Discipline -- psychopharmacology

5. Grade level -- college-med school

6. One line description of lesson --

patient simulation w/ mood-active drugs

LESSON -- ulmc36 HELP available

BLOCK	NAME
a	start
b	vocab+def
c	start.
d	patient
e	driver
f	drive1
g	drive2
h	choice
i	shrink

BLOCK 0 - start SPACE = 192

```
1  ********************************************************************
2  ********************************************************************
3  ********************************************************************
4  ***
5  ***      please send this printout via
6  ***      intercampus courier service
7  ***                        to
8  ***      mike obrien
9  ***      221 ses
10 ***      chicago circle campus
11 ***
12 ***
13 ********************************************************************
14 ********************************************************************
15 ********************************************************************
```

BLOCK b = vocab+def SPACE = 146

```
 1  vocabs   drugs
 2           <a,an,the,it,is,of,to,administer,inject,prescribe;gi
             ve,require,check,look,at
 3           care,bed,for,today,intravenous,iv,IV,call,consult
 4           all,administering,giving,injecting,send,see
 5           refer,him
 6           >
 7           (amphetamine,benzedrine,speed,upper,uppers),(imipram
             ine,tofranil)
 8           (chlorpromazine,thorazine),(miltown,meprobamate)
 9           (pulse,heartbeat,temp,temperature,vital*signs,signs)
10           (glucose,sugar),rest,(psychiatrist,psychiatric,shrin
             k),(restraints,restraint)
11           (leave,go*home,done,nothing),(stop,withdraw,remove,h
             alt),(drugs,medication,drug)
12           (change),(dose,change*dose),(cdr,change*drugs)
13  zero     v1,150
14  define   drugs,daze=v9,signs=v2,temp=v3,pulse=v4
15           resp=v5,bp1=v6,bp2=v7,weight=v8,oldday=v10,drug=v11
16           wd=5 $# answer for "stop drugs" (end of drug list)
17           dose=v12,dim1=v13,dim2=v14,choice=v15,ipulse=v16
18           iresp=v17,ibp1=v18,ibp2=v19,iweight=v20,itemp=v21
19           mood=v22,n=v23,k=v24,start=v25,fact=v26
20           otemp=v27,oresp=v28,opulse=v29,obp1=v30,obp2=v31
21           oweight=v32,temps=v33,resps=v34,pulses=v35,bp1s=v36
22           bp2s=v37,weights=v38,inc=v39,dosepwr=v40,dosecut=v41
23           pulsec=v42,respc=v43,bp1c=v44,bp2c=v45,weightc=v46
24           tempc=v47,oldose=v48,nstart=v49,better=v50,adder=v51
25           nmood=n52
26           dosfac1=(dose/dosecut)**dosepwr,dosfac2=(oldose/dosecu
             t)**dosepwr
```

BLOCK b... vocat+def SPACE = 146

```
1     nmod=n52
2     dostac1=(dose/dosecut)**dosepwr, dostac2=(oldose/dosecu
      t)**dosepwr
3     eval1=ipulse+iresp+itemp+ibp1+ibp2+iweight
4     eval2=(ipulse-ipulse)+(temp-itemp)+2(bp1-ibp1)+3(bp2-
      ibp2)+2(resp-iresp)+.5(weight-iweight)
5     eval3=eval2/(ipulse+itemp+ibp1+ibp2+iweight+iresp)
```

BLOCK c = start SPACE = 100

```
 1  unit    title
 2  size    2
 3  at      606
 4  write   Psychopharmacology:
 5  size    3
 6  at      1517
 7  write   Patient
 8          Simulation
 9  size    0
10  at      2540
11  write   by:  W. D. McDougall
12
13          Programmed by:
14
15               Michael T. O'Brien
16  unit    start
17  at      1110
18  write        Now that you have seen the actions of various
19          drugs upon the chemical activity of neurotransmitter
            s,
20          you may try out your knowledge on some real, live
21          (almost) patients.
22
23               Fundamentally, if you make a mistake, we'd
24          much rather you made it here.
25  do      next
26  unit    tellem
27  next    first
28  at      807
29  write        In the next frame, you will be presented with
30          the case history of your first patient.  You may
```

BLOCK 0 = start SPALL = 100

```
 1  write      In the next frame, you will be presented with
 2             the case history of your first patient.  You may
 3             read his medical history, the psychiatrist's report,
 4             interview the patient directly, or begin treatment,
 5             in any order.  Naturally, we suggest you obtain all
 6             the available information before making your decisio
               n.
 7
 8                  You will find that in most cases where a non-
 9             specific response is expected of you (that is, a
10             response that is not simply a drug name, a number,
11             etc.), that you may communicate directly in clear
12             English.  If a word is not in the vocabulary of this
13             lesson, it will be underlined with u's.  (uuuuu)
14             Misspellings are underlined with =='s.  (=====)
15             In the event that you get one of these markups,
16             simply correct the spelling (if you got ===), or
17             rephrase your response (if you got uuu).
18  do         next
19  unit       next
20  calc       v1=mode
21  mode       rewrite
22  at         3225
23  write      Press -NEXT-.
24  mode       v1,erase,rewrite,write
25  unit       back
26  calc       v1=mode
27  mode       rewrite
28  at         3118
29  write      Press -BACK- to review.
30  mode       v1,erase,rewrite,write
```

BLOCK 6 - start SPACE = 100

1 write Press Enter to review.
2 mode vi,erase,rewrite,write

```
        BLOCK d - patient                          SPACE = 105
 1  unit     first
 2  calc     temp=:temp>=99
 3           it=mp >=98.6
 4           pul=:=pul=:=120
 5           ipulse>=60
 6           bp1>=bp-1>180
 7           ibp1=:120
 8           bp2=:dbp2>=90
 9           ibp2>=70
10           resp>=oresp>=35
11           iresp>=20
12           weight>=oweight=:120
13           iweight>=125
14           daze>=0
15           mood=5
16           inc>=1
17           drug>=-1
18           olddays=-7
19  do       pattell
20  at       130
21  write    Patient Data
22  at       810
23  write    Patient exhibits symptoms indicative of incipient
24           paranoid schizophrenia.  Has attempted suicide twice
25           in the past two months.  Committed on order of state
26           circuit court, upon pleading guilty to the murder of
27           his grandmother.  His explanation: "The old bag was
28           trying to poison me.  I know she was!"
29  at       3101
30  write    -LAB- for psychiatrist's report
31           -DATA- for medical history
```

```
      BLOCK d - patient                          SPACE - 105
 1  write    -LAB- for psychiatrist's report
 2           -EXAM- for medical history
 3  at       3135
 4  write    -NEXT- for treatment section
 5  lab      shrink
 6  data     history
 7  next     driver
 8  unit     shrink
 9  do       pattell
10  at       135
11  write    Psych Report
12  at       810
13  write    Patient is a dangerous schizophrenic, but cannot
14           be treated until calmed.  Is almost totally out
15           of touch with reality at present.
16  do       next
17  end
18  unit     history
19  do       pattell
20  at       135
21  write    Med History
22  at       810
23  write    Patient is thin, pale, shows bad muscle tone but
24           does not appear to exhibit any serious allergies.
25           Care is advised in administering medication.
26           Extreme myopia is present.  Patient stutters.
27  do       next
28  end
29  unit     pattell
30  at       150
31  write    [AY = is,daze]
```

BLOCK d - patient SPACE = 105

```
1  at        153
2  write     DATE = 12.dow:d
3  at        181
4  write     NAME:  Forepaugh, Jason P.
5            AGE:  27
6            HEIGHT:  5' 11"
7            WEIGHT:  it,weight,3.0i
8  draw      216,511;428;401;skip:400,511;151;511,496
```

BLOCK = driver SPACE = 21

```
 1  unit    driver
 2  help    choice
 3  do      pattell
 4  do      pattelll
 5  do      patsp4k
 6  at      13ø
 7  write   Treatment Section
 8  at      131ø
 9  write   What do you want to do, doctor?
10  at      3118
11  write   Press -NEXT- for new day.
12  at      3201
13  write   -HELP- Available.
14  at      3224
15  write   Press -DATA- for patient's vital signs.
16  arrow   1512
17  eraseu  resp1
18  jkey    data
19  specs   nookno,okspell,bumpshift
20  do      resp
21  do      judged=1$and$vocab=-1,sorry.x
22  wrong
23  goto    key=date,sign,x
24  do      increm
25  concept amphetamine
26  concept chlorpromazine
27  concept imipramine
28  concept meprobamate
29  concept withdraw drugs
30  concept pulse
31  goto    signs
```

BLOCK 4 - driver SPACE = 21

```
 1  concept pulse
 2  goto    signs
 3  concept psychiatrist
 4  jump    psych
 5  concept done
 6  do      increm
 7  concept dose
 8  inhibit erase
 9  jump    drug,x,newdose
10  write   You can't change doses; no drug is being given!
11  eraseu  clcd
12  concept cdr
13  write   You have to stop medication and wait a week;
14          you can't just change drugs immediately.
15  eraseu  clcd
16  concept change
17  write   But what do you want to change?
18  eraseu  clcd
19  endarrow
20  unit    sorry
21  at      2012
22  write   Sorry, but I do not understand.
23          Try rephrasing.
24  unit    noword
25  at      1714
26  write   There's a word here I don't know ('uuuuu').
27  unit    nospell
28  at      1814
29  write   There's a word misspelled here ('********').
30  unit    nophrase
31  at      1914
```

BLOCK e - driver SPACE = 21

```
 1  unit    nophrase
 2  at      1914
 3  write   There's an incomplete phrase here (******).
 4  unit    someone
 5  at      1712
 6  write   You're already using that drug!
 7  unit    increm
 8  goto    -signs,x,sendback
 9  add1    daze
10  calc    signs=0
11  do      update
12  calcs   drug=2,adder=(opulse-ipulse)/eval1,0
13  calc    mood=15.23(eval3-adder)-3.5
14  calcs   mood,mood=-1,,,,,,,,7
15  calcs   (nmood=mood)=3,better=better+1,0
16  jump    better=5.done,x
17  do      check
18  jump    driver
19  unit    resp
20  do      vocab,x,noword
21  do      spell,x,nospell
22  do      phrase,x,nophrase
23  do      ansent,x,response
24  unit    resp1
25  mode    erase
26  do      resp
27  do      signs,x,sendback
28  do      judged,x,x,sorry
29  do      ansent=md,umdrug,x
30  mode    write
31  unit    response
```

BLOCK 4 - driver SPACE = 21

```
 1  mode     write
 2  unit     response
 3  judge    wrong
 4  goto     ansent(wd$and$drug=-1,j,x
 5  goto     drug=ansent,someone,x
 6  goto     ansent(wd$and$drug=-1,nonew,x
 7  goto     ansent wd$and$daze-oldday<7,notyet,x
 8  goto     ansent=wd$and$drug=-1,contwd,x
 9  calcs    oldday,oldday=0,, $$clear at first drug
10  calcs    drug,drug=ansent,,  $$set drug
11  calcs    ansent=wd,start=nstart:daze,, $$remember when drug s
             tarted
12  goto     ansent=wd,nodrug,x $$remove drug
13  inhibit  erase
14  jump     ansent(wd,newdose,x
```

```
      BLOCK 1 = drivel                    SPACE =  65
 1   unit    * update
 2   goto      drug,none;*
 3   calcs     drug,dosecut:,,,10^5,5500,700,5500
 4   calc      dosepow=1./(ln(150/1500)/ln(150/dosecut))
 5   calcs     drug,A=,,,75,12,10^6,12
 6   calcs     drug,k=,,,,.8,.8,10^-6,,.8,,
 7   calcs     drug,pulsec=,,,-7,-13,3.2,-7,,
 8   calcs     drug,respc=,,,8,-4,.7,-4,,
 9   calcs     drug,bp1c=,,,20,-28,-8,-14,,
10   calcs     drug,bp2c=,,,10,-10,-2,-7,,
11   calcs     drug,weightc=,,,,-1,.05,.05,.05,,
12   calc      fact=A((dosfac1)(1-exp(-k(daze-nstart)))-(dosfac2)(1
                -exp(-k(daze-nstart-1))))
13             pulse=pulse+pulsec*fact
14             resp=resp+respc*fact
15             bp1=bp1+bp1c*fact
16             bp2=bp2+bp2c*fact
17             weight=weight+weightc*fact
18             oldose=dose
19   unit      newdose
20   calc      oldose=dose
21   next      driver
22   at        2012
23   write     What daily dose do you want to give (in mg)?
24   arrow     2210
25   store     dose
26   write     Give a simple number, please.
27   wrongv    0,0
28   write     You must specify some dose!
29   answ      500,500
30   write     You may request a change of dose later if you wish.
```

```
      BLOCK 1 = drivel                          SPACE =  65
 1    ansv     500,500
 2    write    You may request a change of dose later if you wish.
 3    calcs    dose=olddose,nstart=doze,,
 4    next     driver
 5    wrongv   10000,10000
 6    write    That's too much!
 7    no
 8    unit     patvell1
 9    at       501
10    write    drug=
11    writec   drug,none,,,amphetamine,chlorpromazine,imipramine,
12             meprobamate,,
13    draw     421;521;501
14    at       601
15    writec   drug,,started (s,daze-start) days ago
16    at       701
17    writec   drug,,dose = (s,dose) mg/day
18    do       drug,x,nline
19    unit     nline
20    draw     601;621;521
21    draw     619;719;701
22    unit     ridmess
23    at       2512
24    erase    40,3
25    unit     nodrug
26    calcs    drug,ing$,,,5,9,8,10
27    calc     drug$=-1  $$remove drug
28             olddav$=daze  $$remember when drug removed
29    do       wnodrug
30    unit     wnodrug
31    at       1714
```

BLOCK 1 - drive1 SPACE = 65

```
 1  unit     undrug
 2  at       1714
 3  write    Medication stopped.
 4  unit     normal
 5  at       2212
 6  write    You must take the patient off medication and wait
 7           for at least a week before you can start him on
 8           a new drug!
 9  unit     notyet
10  at       2012
11  write    You haven't waited long enough for a new drug yet!
12  unit     cantwd
13  at       2312
14  write    You can't withdraw medication since the patient
15           doesn't have any prescribed yet.
16  next     driver
17  unit     sendback
18  at       2212
19  write    You can't go home for today without
20           checking the patient's vital signs!
```

BLOCK 9 = drive2 SHARE = 139

```
 1  unit    none
 2  calc    temp:temp+(rate*(totemp-temp)/inc
 3          resp:resp+(rate*(tresp-resp)/inc
 4          bp1:bp1+(rate*(tbp1-bp1)/inc
 5          bp2:bp2+(rate*(tbp2-bp2)/inc
 6          pulse:pulse+(rate*(tpulse-pulse)/inc
 7          weight:weight+(rate*(tweight-weight)/inc
 8  unit    check
 9  jump    (pulse>30)(pulse<200),x,dead,x
10  jump    (temp>95)(temp<108),x,dead,x
11  jump    (resp>15)(resp<70),x,dead,x
12  jump    (bp1>80)(bp1<260),x,dead,x
13  jump    (bp2>30)(bp2<130),x,dead,x
14  unit    dead
15  size    3
16  at      510
17  write   Your patient is
18  size    7
19  at      1317
20  write   DEAD!
21  size    0
22  at      1815
23  write   Vital Signs at Time of Demise were:
24  at      2025
25  write   pulse = is.pulse:
26          resp = is.resp:
27          temp = is.temp:
28          blood pres. = is.bp1:/is.bp2:
29          weight = is.weight:
30  at      2612
31  write   Death occured on day is.daze: of treatment.
```

BLOCK 5 - drive2 SPACE = 134

```
 1  at        2612
 2  write     Death occured on day 13,dose of 1 treatment.
 3            Further inquiries may be made at the morgue.
 4  unit      clod
 5  eraseu    resp1
 6  at        1714
 7  erase     50,2
 8  unit      signs
 9  calc      signs>-1 $$ to make sure he does this
10  draw      151;143;743;511,400
11  at        245
12  write     pulse = (t,pulse,3.0)
13            resp = (t,resp,2.0)
14            temp = (t,temp,3.0)
15            bld. press.
16                 = (t,bp1,3.0)/(t,bp2,3.0)
17            weight = (t,weight,3.0)
18  judge     ignore
19  unit      dosepur
20  term      d
21  at        1012
22  write     dose =
23  arrow     1019
24  store     dosepur
25  ok
26  jump      first
27  unit      dosecut
28  term      dc
29  at        1010
30  write     dosecut=
31  arrow     1019
```

BLOCK 8 - drive2 SPACE = 139

```
1  write   dskout
2  arrow   1819
3  store   dskout
4  ol.
5  jump    first
```

```
        block 6: choice                              SPACE =  70
 1  unit    choice
 2  at      1012
 3  write   Pick the number of your choice:
 4
 5          1) List of available drugs
 6          2) List of available treatments
 7  arrow   1515
 8  long    1
 9  store   choice
10  ansv    1.5,.5
11  next    choice,x,x,druglist,tretlist,>
12  at      3225
13  write   Press -NEXT-.
14  no
15  write   Only one of the available items, please!
16  unit    druglist
17  at      505
18  write   Amphetamine:
19  draw    where-12:where
20  write     Stimulant of the central nervous system:
21          Very powerful and fast-acting.
22          Dose runs from small (5-? mg dose to overdose
23          (300-1000 mg dose).  (Also known as Benzedrine.)
24
25          Chlorpromazine:
26  draw    where-15:where
27  write     Fast-acting tranquilizer:
28          Dose runs from small (100 mg dose to overdose
29          (1000 mg dose).  (Also known as Thorazine.)
30
31          Imipramine:
```

```
BLOCK h = choice                                SPACE =  711
 1
 2              Imipramine:
 3  draw        where 11;where
 4  write         Very slow acting stimulant and anti-depressant:
 5              Take from 2-4 weeks for great effect.  Dose runs
 6              from small (100 mg/day) to overdose (600 mg/day).
 7              (Also known as Tofranil.)
 8
 9              Meprobamate:
10  draw        where-12;where
11  write         Medium-speed tranquilizer:
12              Dose runs from small (100 mg/day) to overdose
13              (1000 mg/day).  (Also known as Miltown.)
14  end
15  unit        tretlist
16  back        druglist
17  at          810
18  write       While you are on the main treatment page, you may:
19
20              1) Prescribe one of a series of drugs for the
21              patient; the list of drugs may be seen as the
22              other option on the main -HELP- page (or you may
23              press -EMO- to see it now).
24
25              2) Ask for a psychiatrist to interview the patient
26              and give you a report on his success in treating
27              the patient in the patient's current state.
28
29              3) Stop giving medication that has already been
30              prescribed (you must halt medication for seven
31              days before you can start administering a new drug).
```

```
        BLOCK h - choice                    SPACE = 70
1               prescribed (you must halt medication for seven
2               days before you can start administering a new drug).
3
4               4) md to see the patient's vital signs (you should
5               do this every day!).
6   at          3210
7   write       Press  NEXT- to return to the treatment page.
8   end
```

```
      BLOCK 1 = shrink                    SPACE = 100
 1  unit    psych
 2  next    driver
 3  at      1312
 4  write   Psychiatrist Reports:
 5  at      1512
 6  writec  mood=What's the big idea of sending me an unconsciou
            s
 7          body to interview??*
 8          Interview useless!  Patient kept falling asleep
 9          on the couch!*
10          Patient rather drowsy, extremely difficult to
11          communicate with.*
12          Patient somewhat drowsy, but otherwise fairly
13          rational.  Interviewing difficult but somewhat
14          productive.*
15          Patient seems to be calm.  Interviewing proceeding
16          satisfactorily.*
17          Patient is rather excited.  Interviewing possible
18          but difficult.*
19          Patient is extremely active and excited.  Normal
20          conversation almost impossible.*
21          Patient is hallucinating!  No normal communication
22          possible.*
23          (Patient never made it to psychiatrist's office.
24          Broke away from interns and went tearing through
25          the hospital.
26  unit    patspek
27  at      812
28  write   Patient's comment's for today:
29  at      1012
30  writec  mood=Zzzzzzzz.....*
```

BLOCK 1 Shrink SPACE = 108

```
 1  at        1012
 2  write     mood$Drowsy.....$
 3            Huh?  Whazzat?  Who'd you say?$
 4            I'm feeling sleepy, but a little rest might fix
 5            me up.$
 6            Not too bad today, but I'm a little sluggish.$
 7            Say, I'm feeling pretty good today, Doc!$
 8            Gee, yeah!  Hey!  I really feel great today!$
 9            Oh, wow!  (*twitch*)  Far out!$
10            Hey, help me pick these pink clouds off the
11            ceiling!$
12            (Patient incommunicado.  Attempting to join a flock
13            of birds outside his window.)
14  unit      done
15  at        1212
16  size      2
17  write     Congratulations!
18  size      0
19  at        1515
20  write     The patient's condition has been stabilized at
21            a treatable level for five days.
22            You've done your job well!'
23  end       lesson
```

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